Childhood and Behavioral Disorders

Steven C. Stoner, Pharm.D., BCPP

Clinical Associate Professor of Pharmacy Practice

UMKC Schools of Pharmacy and Medicine

Northwest Missouri Psychiatric Rehabilitation Center

Director, ASHP Accredited Psychopharmacy Residency

Attention Deficit Hyperactivity Disorder

History of ADHD

- Post encephalitic disorder
- Hyperkinetic / impulsive disorder
- Minimal brain disorder
- Hyperkinesis
- ADD with or without hyperactivity

ADHD

Six or more of the following symptoms have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level. (Present before age 7 / 2 or more settings.)

- **Inattention**
  - –Fail to give attention to details
  - –Difficulty sustaining attention
  - –Does not listen
  - –Fail to complete tasks
  - –Difficulty organizing tasks
  - –Avoids taks requiring sustained mental effort
  - –Loses things necessary for tasks / forgetful
  - –Easily distracted
- **Hyperactivity**
  - –Difficulty sitting still
  - –Excessive running or climbing
  - –Problems engaging in leisure activity
  - –Excessive talk
  - –“On the go”….
- **Impulsivity**
  - –Classroom disruptions
  - –Difficulty waiting turn
  - –Intrusiveness

Diagnostic and Statistical Manual for Mental Disorders (DSM-IV-TR), American Psychiatric Association, 2000.

ADHD Assessment

- Clinical Diagnosis…there is no test
- Parent Interview
- Patient Observation
- School-Related Assessment
- Rating Scales
  - Child Behavior Checklist
  - Teacher Report Form
  - Conners Parent and Teacher Rating Scales

J Am Acad Child Adolesc Psychiatry, 1997; 36:10.

ADHD Epidemiology

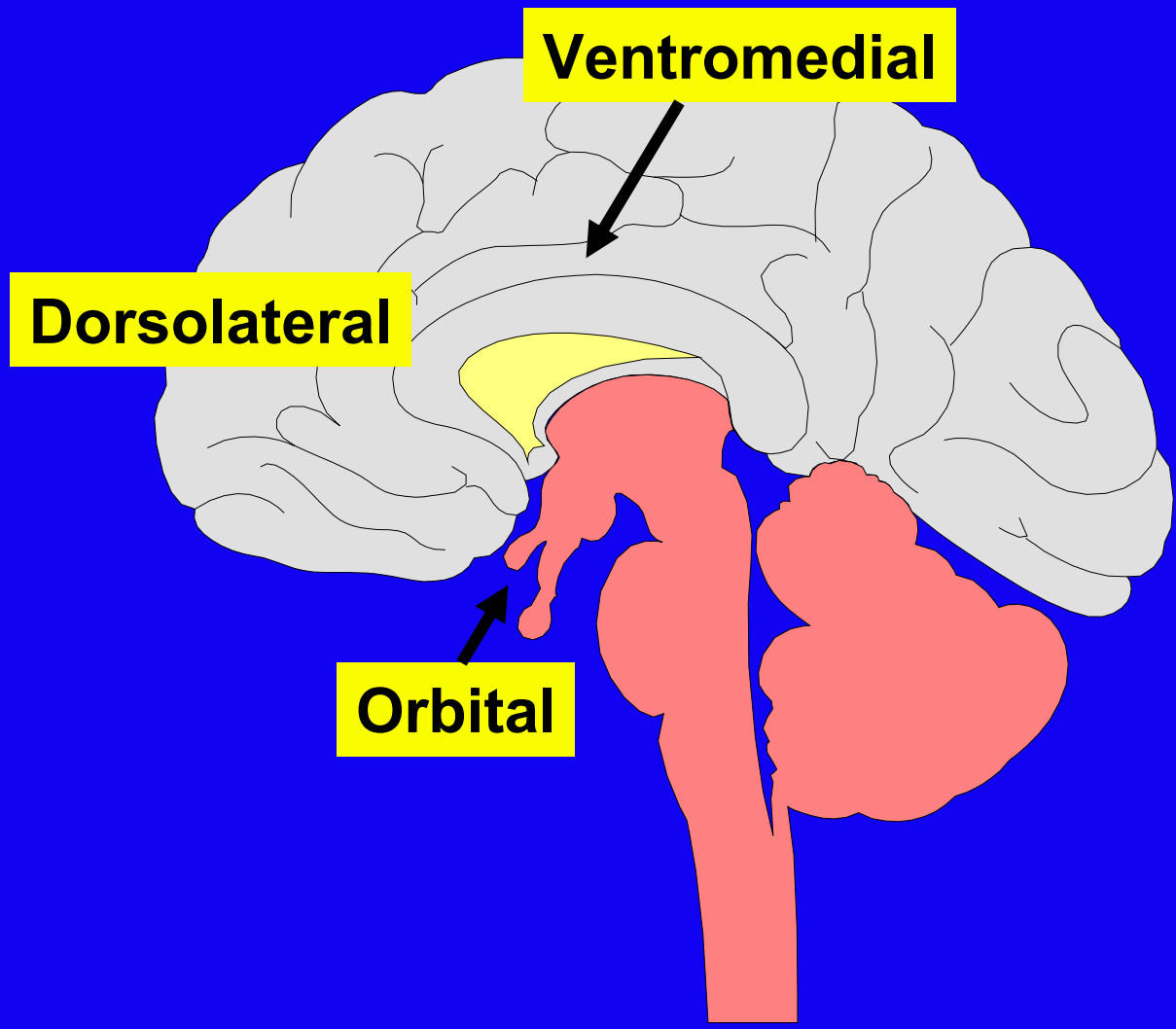
- 3-5 % of children
  - may be overdiagnosed (20%), but only 10-15% who meet diagnostic criteria receive treatment
- Male to female ratio
  - 4:1 hyperactive-impulsive type
  - 2:1 inattentive type
- Adulthood
- Chronicity
- Comorbidity
  - Conduct and oppositional, anxiety, and depression

J Am Acad Child Adolesc Psychiatry, 1997; 36:10.

ADHD Etiology

- Genetic Link
- Environmental Factors
- Dopamine/Norepinephrine
  - Barkley's Concept
    - Impaired response inhibition resulting in difficulty self-regulating….mediated by underfunctioning of the orbital frontal cortex and subsequent connections to the limbic system
  - prefrontal cortex
    - executive functioning ("self-control")

Zametkin AJ, Liotta W. J Clin Psychiatry, 1998; 59[suppl 7]: 17-23.
Barkley RA. Psychol Bull, 1997; 121: 65-94.
Barkley RA. J Am Acad Child Adolesc Psychiatry, 2000: 39:8.


Ventromedial
Dorsolateral
Orbital

Pharmacologic Management of ADHD

Initiating Pharmacotherapy

- Diagnostic Criteria Met
- Balance Risks vs. Benefits
- Establish Baseline for Symptoms
- Don’t Ignore Other Therapeutic Interventions (behavioral modification)
- Proper Medication Administration and Compliance
- Education of the Caregiver and Child

J Am Acad Child Adolesc Psychiatry, 1997: 36:10.

ADHD: Stimulants

- **Methylphenidate (Ritalin®, Ritalin SR®, Ritalin LA®)**
  - immediate and sustained release tablets
  - Combination immediate release and enteric coated delayed release
- **Methylphenidate (Concerta®)**
  - OROS triple-layered drug delivery system (extended release)
- **Methylphenidate (Metadate CD and Metadate ER®)**
- **Dextroamphetamine Sulfate, Dextroamphetamine Saccharate, Amphetamine Sulfate, Amphetamine Aspartate (Adderall® and Adderall XR ®)**
  - 75:25 ratio of dextro and levo-amphetamine
- **Dextroamphetamine (Dexedrine®)**
- **Dexmethylphenidate (Focalin®)**
- **Pemoline (Cylert®)**
- **Atomoxetine (Strattera®)**

Stimulant Availability

- Methylphenidate (Ritalin®, Ritalin SR®, Ritalin LA®)
  - Available: 5 mg, 10 mg, and 20 mg tablets
  - Available: 20 mg sustained release tablet (SR)
  - Available: 20 mg, 30 mg, 40 mg capsules (LA)
- Methylphenidate (Concerta®)
  - OROS triple-layered drug delivery system
  - Available: 18 mg, 27 mg, 36 mg, and 54 mg caplets
- Methylphenidate (Metadate CD® / Metadate ER ®)
  - Available: 20 mg capsule / 10 and 20 mg tablets
- Atomoxetine (Strattera®)
  - Available: 5 mg, 10 mg, 18 mg, 25 mg, 40 mg, and 60 mg capsules
- Dexmethylphenidate (Focalin ®)
  - Available: 2.5 mg, 5 mg, and 10 mg tablets

Stimulant Availability

- **Dextroamphetamine Sulfate and Saccharate, Amphetamine Sulfate and Aspartate (Adderall®)**
  - **Available: 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, and 30 mg tablets**
  - **Double-scored tablets**
- **Dextroamphetamine Sulfate and Saccharate, Amphetamine Sulfate and Aspartate (Adderall XR®)**
  - **Available 10 mg, 20 mg, and 30 mg capsules**
  - **(Immediate and Delayed Release Beads)**
- **Dextroamphetamine (Dexedrine®)**
  - **Available: 5 mg, 10, mg, and 15 mg sustained release capsule**
  - **Available: 5mg and 10 mg tablets**
  - **Available: 5 mg/ 5 ml elixir**
- **Pemoline (Cylert®)**
  - **Available: 18.75 mg, 37.5 mg, and 75 mg tablets**
  - **Available: 37.5 mg chewable tablet**

Concerta®

- Extended-release methylphenidate
  - OROS® sustained release dosage form
    - Semipermeable rate-controlling membrane surrounding an osmotic inner core (tri-layered with immediate release overcoat)
  - Caution: GI narrowing / glaucoma
- Pharmacokinetics
  - Designed for 12-hour effect
  - Ritalin SR® 20 mg / Ritalin® 5 mg tid vs. Concerta®

(see next slide)

- Clinical Trials
  - Concerta® vs. Placebo and IR Methylphenidate

Alza Pharmaceuticals Package Insert, 2001: www.concerta.net

Concerta®

	Concerta ® 18 mg q day (n = 36)	Methylphenidate 5 mg po tid (n = 35)
$C_{max\ (ng / ml)}$	3.7 ± 1.0	4.2 ± 1.0
$T_{max\ (h)}$	6.8 ± 1.8	6.5 ± 1.8
$AUC_{inf\ (ng – h / ml)}$	41.8 ± 13.9	38.0 ± 11.0
T ½ (h)	3.5 ± 0.4	3.0 ± 0.5

Alza Pharmaceuticals Package Insert, 2001: www.concerta.net

Concerta® Conversion

Previous MPH Dose	Recommended Concerta® Dose
5 mg po bid or tid (IR) 20 mg po a day (SR)	18 mg po a am
10 mg po bid or tid (IR) 40 mg po q day (SR)	36 mg po a am
15 mg po bid or tid (IR) 60 mg po q day (SR)	54 mg po a am

Alza Pharmaceuticals Package Insert, 2001: www.concerta.net

Metadate ER® / Metadate CD ®

- ER designed for 8 hour release
- CD contains 30% IR beads and 70% ER beads
- ER available in 10 and 20 mg tablets
- CD available in 20 mg capsules
- Bioavailability
  - More slowly but as extensively absorbed
  - Cmax / Tmax / AUC
  - No significant difference between ER and SR
- Dosing
  - Use in place of immediate release tablets when the 8 hour dosage of Metadate ER® corresponds to titrated 8 hour dose of immediate release tablets

Medeva Pharmaceuticals, Inc.: Package Insert, May 2000.

Ritalin LA®

- Extended release preparation with bi-modal release profile
- SODAS® Technology
  - Spheroidal oral drug absorption system
  - Half of dose is immediate release beads and half of dose is enteric-coated, delayed release beads
  - Initial Cmax and Tmax comparable to IR methylphenidate
  - Lower second peak concentation vs. IR
  - Higher interpeak concentration vs. IR
  - May be sprinkled over food
- Patients converted to dosing form from IR

Dexmethylphenidate (Focalin®)

- Contains the active d- isomer of methylphenidate
- Efficacy maintained at half of Ritalin dose
- Inhibits reuptake of NE/DA into presynaptic neuron and increases release of these monoamine neurotransmitters
- Tmax = 1.1 hours
- Dosing: Start 2.5 mg po bid, titrate to maximum of 20 mg per day
- Available: 2.5 mg, 5 mg, and 10 mg tablets “D shaped”

ADHD: Stimulants

Medication	Dosage Range** (mg / kg/ day)	Max Dosage (mg / day)	Dose Interval
MPH	0.3 - 0.6	60	qday-bid-tid
Dex	0.15 - 0.3	40	bid-tid
Dex/Amphet	N/A	40	q day - bid
Pemoline	0.5 - 3	112.5	q day

Children 3-5 years of age start at 2.5 mg po q day

Children 6 years of age and older start at 5 mg q day to bid

**many physicians prefer mg/day dosing vs. weight based model

J Am Acad Child Adolesc Psychiatry, 1997; 36:10.
Rapport MD, Denney C. J Am Acad Child Adolesc Psychiatry, 1997; 36:4

ADHD Treatment Algorithm

Texas Children's Medication Algorithm Project

Stage 0 - Diagnostic Assessment (psychometric assess)

Stage 1 - monotherapy with methylphenidate or dextroamphetamine

Stage 2 - if non-response use different stimulant

Stage 3 - if non-response use alternate stimulant (pemoline)

Stage 4 - if non-response try antidepressant bupropion, imipramine, nortriptyline

Stage 5 - if non-response try different antidepressant

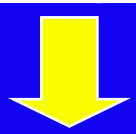
Stage 6 - if non-response try alpha agonists

***** If response obtained at any stage continue therapy into continuation and maintenance phases (1-2 years)***

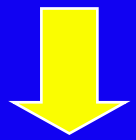
J Am Acad Child Adolesc Psychiatry 2000; 39(7).

ADHD Comorbid Anxiety/Depression
Texas Children's Medication Algorithm Project

- **Stage 0 - Diagnostic Assessment**



- **Stage 1 - Stimulant monotherapy X 2 weeks**
  - **(methylphenidate, dextroamphetamine, or mixed amphet salts)**



- **Stage 2 - ADHD improved but not MDD**
  - **continue stimulant and add antidepressant**

- **Stage 2 - Neither ADHD or MDD improved**
  - **begin antidepressant without stimulant, consider stimulant if MDD responds and ADHD does not**

J Am Acad Child Adolesc Psychiatry 2000; 39(7).

ADHD Comorbid Tic Disorder

Texas Children's Medication Algorithm Project

- Stage 0 - Diagnostic Assessment
- Stage 1 - Stimulant monotherapy
- Stage 2
  - if tics increase or if ADHD does not respond try another stimulant;
  - if tics do not increase add alpha agonist (clonidine or guanfacine)
- Stage 3 - if tics do not respond consider risperidone
- Stage 4 - if tics do not respond consider pimozide
- Stage 5 - if tics do not respond consider haloperidol

J Am Acad Child Adolesc Psychiatry 2000; 39(7).

ADHD with Intermittent Explosive Disorder
Texas Children's Medication Algorithm Project

- Stage 0 - Diagnostic Assessment
- Stage 1 - Stimulant monotherapy
- Stage 2
  - If ADHD does not respond try another stimulant
  - If aggression does not subside add mood stabilizer (lithium, divalproex, carbamazepine) or alpha agonist
- Stage 3 - If aggression persists try different agent from Stage 2
- Stage 4 - Consider an atypical antipsychotic
  - risperidone, olanzapine, quetiapine, clozapine

J Am Acad Child Adolesc Psychiatry 2000; 39(7).

ADHD Stimulant Responders

- **No identified predictors of response**
  - HVA levels
  - Decreased volume of left caudate, higher reversed caudate asymmetry, smaller right anterior-superior white matter
- **Motor Effects**
  - Reduce activity to normal
  - Improve handwriting and fine motor control
- **Social Effects**
  - Decrease anger
  - Improve ability to play
- **Cognitive Effects**
  - Improved sustained attention
  - Reduce distractibility

Semrud-Clikeman A, et al. J Am Acad Child Adolesc Psychiatry, 2000; 39:4.

ADHD: Stimulant Side Effects

- Insomnia
- Anorexia
- Weight Loss
- Nausea
- Hypertension (1-4 mm Hg)
- Tachycardia (2-6 bpm)
- Headaches
- GI Complaints
- Growth Suppression
- Tic Development
- Psychosis / Mania
- Dermatological
- Lowering of seizure threshold

ADHD: Stimulant Drug Interactions

- Monoamine oxidase inhibitors
- Tricyclic antidepressants
  - Pharmacodynamic and Pharmacokinetic
- Warfarin
  - Enzyme inhibitory effects
- Clonidine with methylphenidate
  - Sudden deaths
- OTC Cold Preparations with stimulants
- Valproate with methylphenidate
  - Dyskinesia ??

Economic Considerations

Medication	Average Daily Dose	Approximate Cost per Month
Ritalin®	40 mg q day	$55.00
Concerta®	36 mg q day	$61.00
Metadate®	40 mg q day	$65.00
Adderall®	30 mg q day	$69.00
Dexedrine®	30 mg q day	$88.00
Cylert®	75 mg q day	$102.00

ADHD: Other Options

- Tricyclic antidepressants
  - imipramine, desipramine, nortriptyline, amitriptyline
- Clonidine
  - conduct and Tourette's disorders
  - second tier treatment for ADHD
- Bupropion
  - positive data in adults and children
- Tyrosine (dopamine precursor)
- Monoamine oxidase inhibitors
- Herbal Remedies ????

J Am Acad Child Adolesc Psychiatry, 1997; 36:10.
J Am Acad Child Adolesc Psychiatry, 2000; 39:2.
J Am Acad Child Adolesc Psychiatry, 2000; 39:7.
Connor DF, et al. J Am Acad Child Adolesc Psychiatry, 1999; 38(12).

Kidalin®

- Catnip - “both relaxing and stimulating”
- Damiana - strengthens the CNS
- Cola - sharpens alertness (= caffeine)
- Lavender - mild tranquilizer
- Chamomile - balances the nervous system
- Periwinkle - increases cerebral blood flow
- Lemon Balm - sedative, mood elevator, antidepressant
- Licorice - suppresses adrenaline release
- Oat Seed - controls emotions

*** No evidence based medicine studies

ADHD Summary

- **Stimulants work to increase both dopamine (dopamine transporter [DAT 1]) and norepinephrine but a complete understanding of their mechanism of action remains unknown.**

- **Stimulants are equally efficacious with similar side effect profiles, but differ in dosage forms available.**

Winsberg BG, Comings DE. J Am Acad Child Adolesc Psychiatry, 1999: 38:12.

ADHD: Commonly Asked Questions

- Does my child need a “Drug Holiday” ?
  - impairment of quality family time
- Can I suddenly discontinue my child’s stimulant medication ?
  - possible rebound hyperactivity
- Is my child going to become a drug addict ?
- What is the best stimulant ?
  - one that works
- Will my child ever grow out of their ADHD ?
  - 50%-65% carry symptoms into adulthood
- Will my child be underdeveloped ?
  - long-term MPH study showed no difference in height or weight

J Am Acad Child Adolesc Psychiatry, 1997: 36:10.
J Am Acad Child Adolesc Psychiatry, 2000: 39:2.
J Am Acad Child Adolesc Psychiatry, 2000: 39:4.

Website Information

- www.addwarehouse.com
- www.chadd.org
- www.additudemag.com
- www.add.org

Substance Abuse

Substance Abuse

A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following occurring within a 12-month period:

1. Failure to fulfill major role obligations at work, school, or home…

2. Use in physically hazardous situations…

3. Recurrent substance related legal problems…

4. Continued use despite persistent or recurrent social or interpersonal problems caused or exacerbated by effects of the substance...

APA: DSM-IV-TR. Washington, DC, 2000.

Substance Dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following occurring at any time in the same 12-month period:

1. Tolerance
2. Withdrawal
3. Larger amounts used over longer period of time…
4. Persistent desire or unsuccessful effort to cut down use…
5. Increased time spent to obtain substances…
6. Important social, occupational, or recreational activities are given up or reduced because of substance use…
7. Substance use is continued despite knowledge of having persistent or recurrent physical or psychological problems likely to have been caused or exacerbated by the substance...

APA: DSM-IV-TR. Washington, DC, 2000.

Adolescent Substance Use

- DSM-IV Criteria
- Alcohol Related:
  - blackouts
  - craving
  - impulsive sexual behavior
- Polysubstance Use
- Comorbid Psychiatric Disorder

Clinical Presentation

- Mood Changes
  - Depression, euphoria
- Cognition Changes
  - Impaired concentration, decreased attention span, disturbances in thinking (delusions)
- Behavior Changes
  - Disinhibition, hypervigilance, somnolence
- Variance with substances

Clinical Presentation

- Impaired psychosocial and academic functioning
  - Family conflict
  - Academic failure
  - Risk-takers
  - Comorbid psychiatric disorder
- Tolerance > Withdrawal
- Preoccupation with use

Substance Use Risk Factors

- Parental Use or “Parenting…the lack of ?”
- Genetic Theories
- Peer attitudes and pressure
- Childhood disruptive behavioral problems
- Environment or Neighborhood
  - Low socioeconomic status
  - High population density
  - Physically deteriorated neighborhood
  - High crime areas

Substance Use Epidemiology

- 90% of high school seniors have tried alcohol
- > 40% of high school seniors have used an illicit substance
- 25% of 8th graders have used alcohol and 12% illicit substances
- Substance use disorders in > 80% juvenile offenders (↓ emotional disorders)
- Adolescent Males > Adolescent Females

Psychiatric Comorbidity

- ADHD
- Conduct Disorder
- Major Depression (↓ suicide risk)
- Anxiety Disorders
- PTSD
- Eating Disorders
- Schizophrenia

Substance Abuse Treatment

- Goal = Abstinence
- Reduce Harm
  - Reduce use
  - Reduce adverse effects
  - Reduce severity and frequency of relapse
  - Improve social or academic functioning

Substance Abuse Treatment

- Intense and adequate duration
- Comprehensive
- Promote family involvement and communication
- Life-style development
- Self-Help groups
- Culturally and economically sensitive
- Aftercare and follow-up treatment

AACAP Practice Parameters. *J Am Acad Child Adolesc Psychiatry* 1997; 36(10).

Pharmacotherapy

- Detoxification
- Withdrawal Management
- Drug Substitution
- Counteract physiological and subjective effects of abused substance
- Treat Comorbid Psychiatric Disorder

Pharmacotherapy

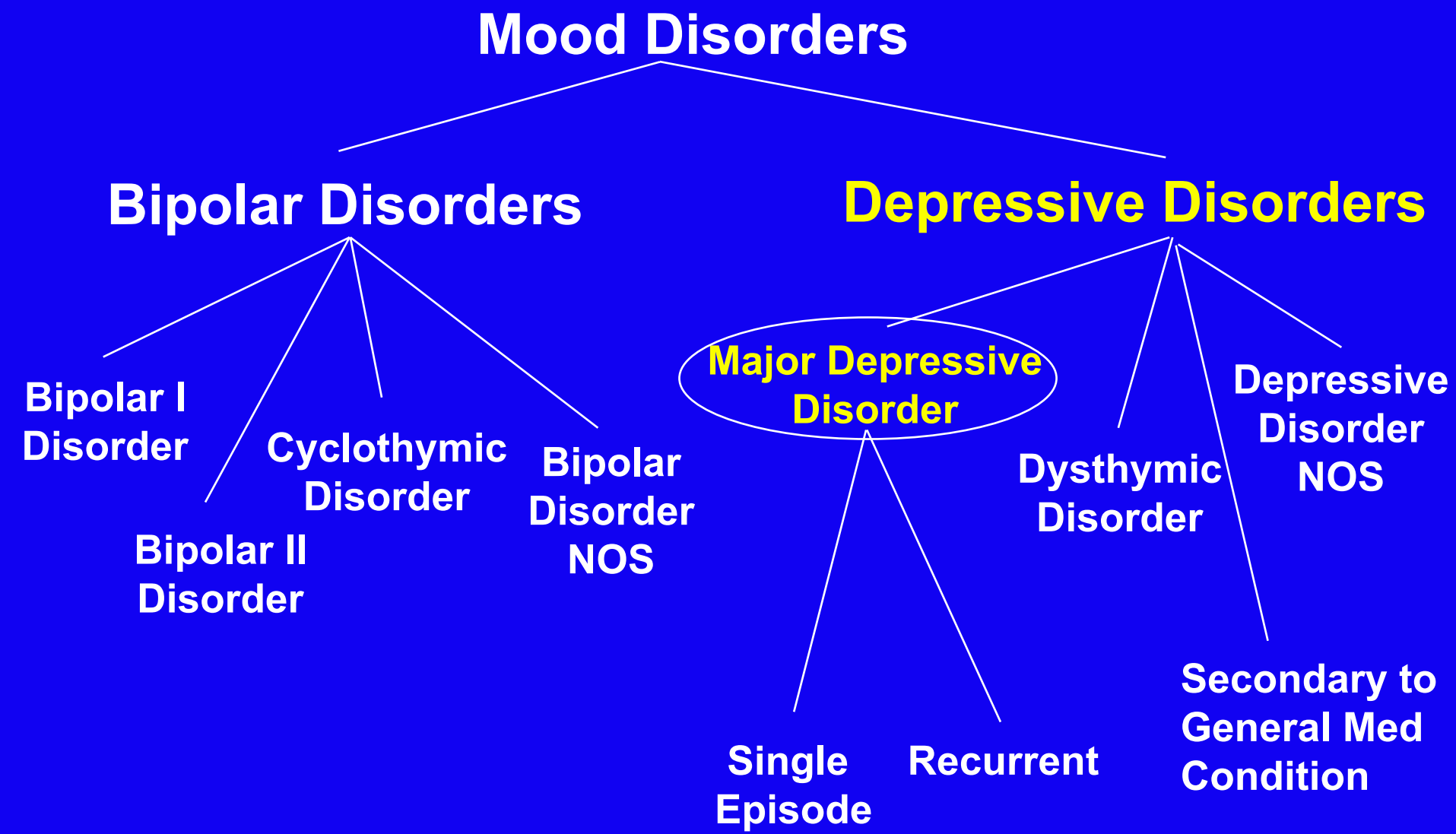
- Withdrawal Management
- Alcohol
- Nicotine
- Opioids
- Cocaine
- Amphetamine

Childhood Depression

Mood Myths

- we all get depressed
- depressed people are weak-willed
- depressed people should “get over it”
- if you ask about suicide the person will attempt it
- antidepressants are addicting
- antidepressants will make you homicidal or suicidal

DSM-IV Classification of Mood Disorders



Major Depression (DSM-IV)®

Five (5) or more of the following symptoms in the same two-week period with at least one being depressed mood or loss of interest or pleasure.

Weight Loss or Gain
Appetite Loss or Gain
Insomnia or Hypersomnia
Psychomotor Agitation
Anergia or Fatigue

Poor Concentration
Suicidal Thoughts
Hopeless or Helpless Feelings
Feelings of Worthlessness or Guilt

Diagnostic and Statistical Manual for Mental Health Disorders (DSM-IV-TR), *American Psychiatric Association, 2000*.

Dysthymic Disorder

- **Depressed mood for most of the day, for more days than not, as indicated subjectively or observed by others for at least 2 years.**
  - **Poor appetite or overeating**
  - **Insomnia or hypersomnia**
  - **Low energy or fatigue**
  - **Low self esteem**
  - **Poor concentration or difficulty making decisions**
  - **Feelings of hopelessness**

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. APA, 2000.

Atypical Depression

- **Applies when the most recent two weeks of major depressive episode or during most recent two years of dysthymic disorder.**
  - **Mood reactivity**
  - **Two or more of:**
    - **Weight gain or increase in appetite**
    - **Hypersomnia**
    - **Leaden paralysis**
    - **Long-standing pattern of interpersonal rejection sensitivity that results in significant social or occupational impairment**

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. APA, 2000.

Diagnosis

Diagnostic Evaluation

thorough history

physical and neurological exam

mental status exam

functional assessment

laboratory tests

diagnosis of inclusion not exclusion

Target Symptoms Physical

- Decreased appetite
- Weight Loss*
- Hyperphagia / weight gain
- Early morning awakening
- Hypersomnia
- Decreased libido
- Psychomotor retardation
- Psychomotor agitation
- General unwellness
- Fatigue
- GI disturbances

Target Symptoms Mood

- Emotional withdrawal*
- Loss of interest in work or hobbies (Anhedonia)
- Loss of motivation
- Low self esteem
- Lack of reactivity (Blunted affect)
- Sad, or blue feelings
- Suicidal ideation
- Guilt/ Self-deprecation
- Psychosis

Target Symptoms Cognitive

- **memory impairment**
- **confusion**
- **poor psychosocial functioning**

Assessing Depression

S - sleep
I - interest
G - guilt

E - energy

C - concentration
A - appetite
P - psychomotor
S - suicide

Questions to Evaluate Depression

- Describe your mood today.
- Do you cry without reason ?
- How is your physical health ?
- What are your hobbies?
- Has your weight changed in the last month?
- Do you have any guilt feelings?

Questions to Evaluate Sleep

- Describe your sleep now and one month ago?
- How many hours do you normally sleep at night and how many do you sleep now?
- What do you do before going to bed?
- What is your sleep like through the night?

Questions to Evaluate Sleep

- When do you wake up?
- Can you fall back to sleep when you wake up?
- Does anything wake you up?
- How long does it take you to fall asleep?
- Do you feel rested in the morning?

Questions to Assess Suicide Risk

- Do you think a lot about death?
- Do you wish you could fall asleep and never wake up?
- Is there hope in your future?
- Do you see a way for your life to improve?

Questions to Assess Suicide Risk

- Have you ever tried to hurt yourself?
- What did you do?
- Do you plan to hurt yourself now?
- How would you do it?
- Do you have the means available to do this?

Major Depression in Children

- Significant source of morbidity and mortality
- 1996-97 there were 792,000 prescriptions for antidepressants written for children aged 6 - 18
- 40,000 children < 5 years old take antidepressants
- Epidemiology

  Prevalence of 3% (children) and 8% (adolescents)

  Mean Duration 32 weeks

  Relapse 72% at 5 years

  >30% develop bipolar disorder

  4 X Increase in Suicide Risk and Substance Abuse
- Early TCA trials not effective over placebo

Major Depression in Children

- Childhood Risk
  - Males = Females
- Adolescent Risk
  - Females 2 X > Males
- Risk Factors
  - Family History
  - Cigarette Smoking
  - Loss of parent or loved one
  - Romantic break-up
  - Attentional, conduct, or learning disability
  - Chronic illness
  - Trauma

Depression Similiarities: Children, Adolescents, Adults

- Sad, irritable mood
- Loss of interest in enjoyable activities
- Change in appetite or weight
- Difficulty sleeping or oversleeping
- Loss of energy
- Psychomotor agitation or retardation
- Feelings of worthlessness or inappropriate guilt
- Difficulty concentrating
- Recurrent thoughts of suicide or death

Depression Specific Symptoms: Children and Adolescents

More pronounced

- Frequent Somatic Complaints
- Social Withdrawal
- Psychomotor Agitation
- Defiance and Disturbances of Conduct (shouting, irritable)
- Talk of running away from home
- Alcohol or substance abuse
- Phobias and Separation Anxiety
- Being bored
- Not playing with friends
- Fear of death
- Rejection sensitivity
- Reckless behavior
- Poor relationship skills

Less pronounced

Hypersomnia
Weight loss
Delusions

Suicide Risk

- Increased risk in adolescent boys if conduct disorder or substance abuse present
- 3rd leading cause of death in 10-24 year olds
- 7% of adolescents with major depression commit suicide in early adult years
- Early diagnosis and intervention important

Treatment Options for Depression

Non-Pharmacological First-Line Treatment Options

- **Cognitive Behavioral Therapy (CBT)**
  - **Change in state of mind by teaching how to look at life with a positive perspective and how to reward self for experiencing pleasant accomplishments.**
  - **Implementation of coping strategies**
- **Psychotherapy**
  - **Similar to CBT**
  - **Goal to change perception of self and behavior**
  - **Usually combined with antidepressant**

Pharmacological Intervention ?

- **Identification of Symptoms of Depression**
- **Factors to Consider**
  - **Severity and dysfunction of the syndrome**
  - **Potential benefits of drug therapy**
  - **Potential risks of drug therapy**
  - **Consequence of not initiating treatment**
  - **Willingness of patient to participate**
- **Don’t place pharmaceutical interventions in a vacuum !!!**

Clinical Situations for Antidepressants

Moderate to severe depression (suicidal)

Psychotic features present

Melancholia

Relapse likely

Bipolar Disorder

Prior history of poor response

Concurrent OCD, PTSD, or Panic Disorder

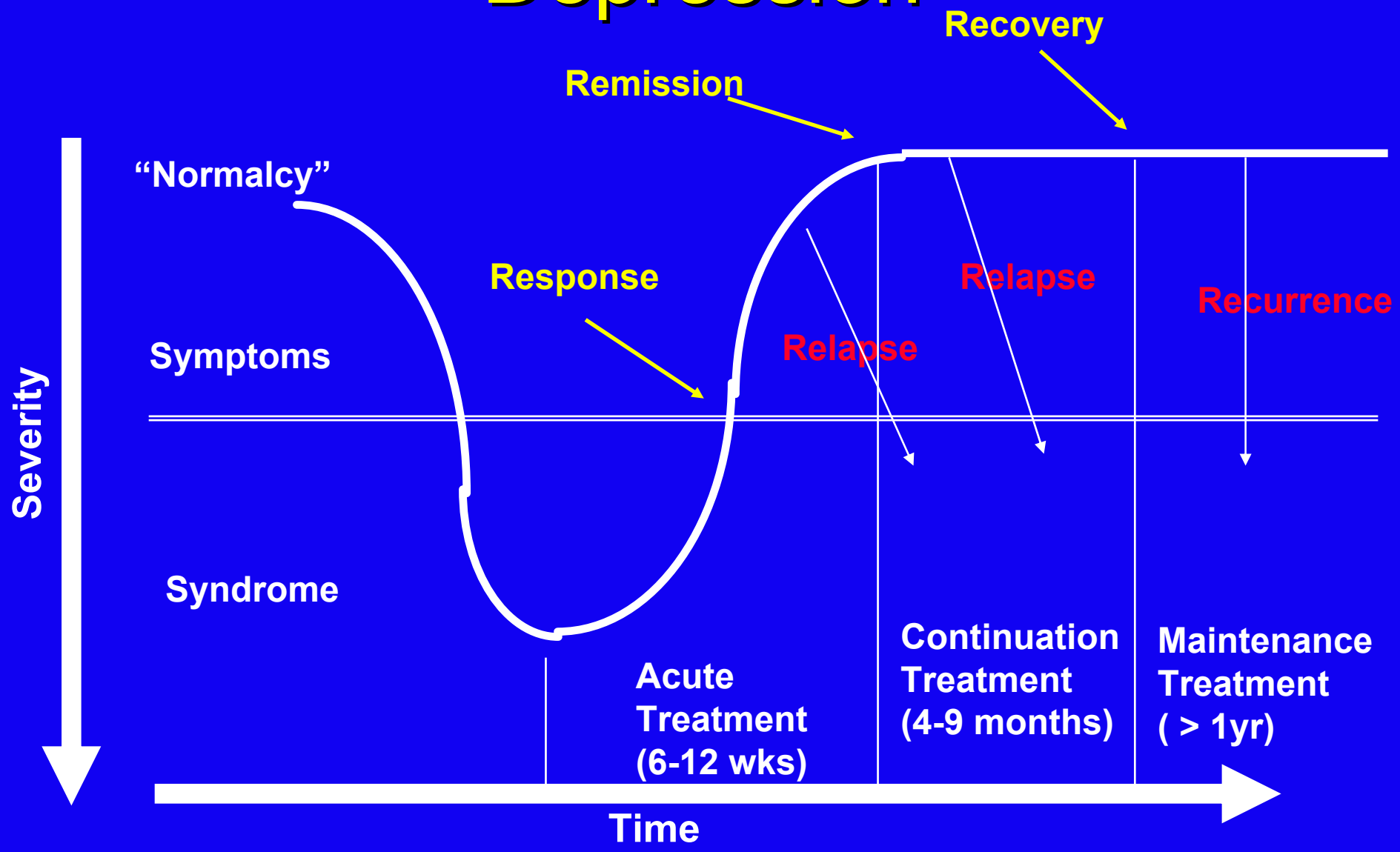
Drug Therapy Selection Principles

- **Presenting Symptomatology**
- **History of Response**
- **Positive Use of Side Effects**
- **Negative Side Effects**
- **Potential for Drug Interactions**
- **Cost and “Where do I send the bill ?”**
- **Age Related Kinetic / Dynamic Considerations**

Goal of Antidepressant Therapy

- **Ultimate: Prevent new episode of depression**
- **Acute Phase**
  - **Initial, quick, short-term response**
  - **Decrease symptoms to nonpathologic level**
- **Continuation Phase**
  - **Maintain improvement, resolve remaining symptoms or functional impairments, prevent relapse**
- **Maintenance Phase**
  - **Prevent recurrence of new episode**

Phases of Treatment for Depression



Adapted from: Depression Guideline Panel, Depression in Primary Care, AHCPR, April 1993.

Course of Response

Antidepressant Maintenance Therapy

- Potential candidates
  - **Three or more episodes of major depression**
  - **Two episodes and :**
    - **+ family history of bipolar depression and major depression**
    - **+ history of recurrence or poor response in continuation phase**
    - **Onset < 20 years of age or > 60 years of age**
    - **Severe episodes, sudden episodes, or life threatening**
    - **Concurrent depression, dysthymia, or anxiety**

Adapted from: Depression Guideline Panel, Depression in Primary Care, AHCPR, April 1993.

Depression Untreated

- **Impaired social and physical functioning**
- **Decreased quality-of-life**
- **Increased morbidity**
- **Increased suicide rates**

J Clin Psychiatry 1999; 60(suppl 6).

Basic Psychopharmacology Principles

- Drugs are not curative, provide symptomatic relief
- Selection of agent is based on potential for toxicity and tolerability, not efficacy
- Treat the symptoms that are present, not the diagnosis
- Ensure adequate length of trial (6-8 weeks)
- Combine drug + non-drug therapy
- Treat through acute, continuation, and maintenance phases
- Individualize treatment approach

Clinical Terminology

Treatment nonresponse

Treatment response

Relapse, Recurrence, Remission

Recovery

Relative treatment resistance

Absolute treatment resistance

Treatment refractory

Adequate dose and length of treatment

Medication intolerance

Response vs. Remission

Partial Response

- 25% to <50% reduction in HAM-D or MADRS scores

Response [≈ 70%]

- > 50% reduction in HAM-D or MADRS scores
- Not equivalent to long-term goal

Remission (2 months of sx below Diagnostic Criteria) [≈ 30 %]

- Best predictor of long-term prognosis, rates decline with time
- < 10 on 21-item HAM-D
- ≤ 7 on 17-item HAM-D
- CGI = 1

Residual Symptoms (> 7 on 17-item HAM-D)

- Strong predictor of relapse, suicide, psychosocial impairment

J Clin Psychiatry 2001; 62 (suppl 16).

Initiation of Therapy

- **Dosing**
  - Underdosing is primary problem with TCAs
  - Initiate therapy with divided doses to minimize ADRs
  - SSRIs can be initiated at therapuetic doses
  - Consider age of patient and adjust accordingly

- **Dosage Adjustment**
  - Target dose should be achieved as quickly as tolerated
  - Improvement in 3-4 weeks of therapy
  - Consider increments/decrements/or alternates in nonresponsive patients
  - Maximal response in 8-12 weeks of therapy

Survival

- **Recurrence rate of 30% in 3 years at full dose, 70% at half dose**
- **50-70% of patients will relapse over 1 year period without maintenance treatment**
- **Risk of relapse continues to increase over time**
- **Risk of relapse significantly reduced with maintenance therapy - 80-90% remain well during first year of maintenance therapy**
- **Psychotherapy does not improve survival significantly over medication management**

•Frank, et.al., *Arch Gen Psychiatry* 1990;47:1093.

•Frank, et.al., *J Affect Dis* 1993;27:139.

•Kupfer, et.al., *Arch Gen Psychiatry* 1992;49:769.

Pharmacotherapy of Depression

- **Monoamine Oxidase Inhibitors (MAOI)**
- **Tricyclic Antidepressants (TCA)**
- Serotonin Selective Reuptake Inhibitors (SSRI)
- **Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)**
- **Serotonin-2 Antagonist / Reuptake Inhibitor (SARI)**
- **Norepinephrine / Dopamine Reuptake Inhibitor (NDRI)**
- **Noradrenergic and Specific Serotonin Antagonist (NaSSA)**
- **Treatment Resistance / Refractory Options**

Stahl SM. J Clin Psychiatry 1998; 59(suppl 4): 5-14.

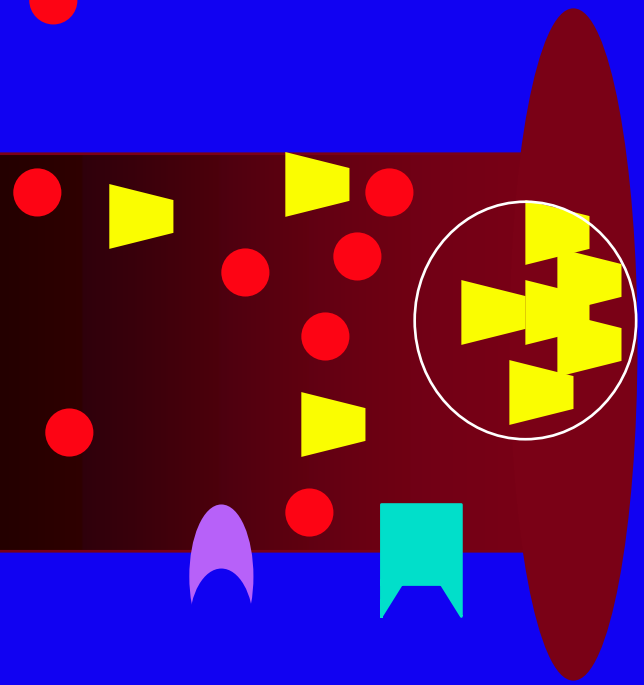
= PRESYNAPTIC RECEPTORS

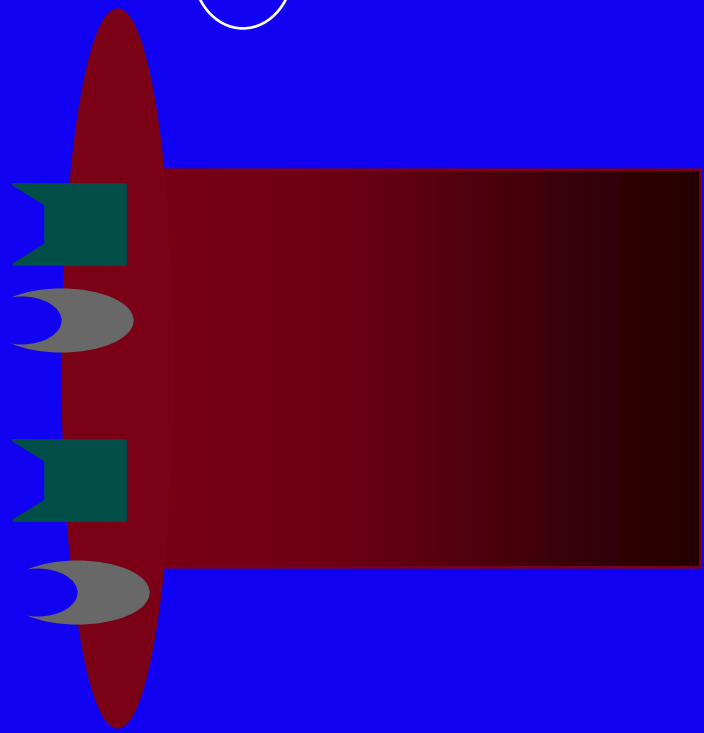
= NEUROTRANSMITTERS

SYNAPSE

= POSTSYNAPTIC RECEPTORS

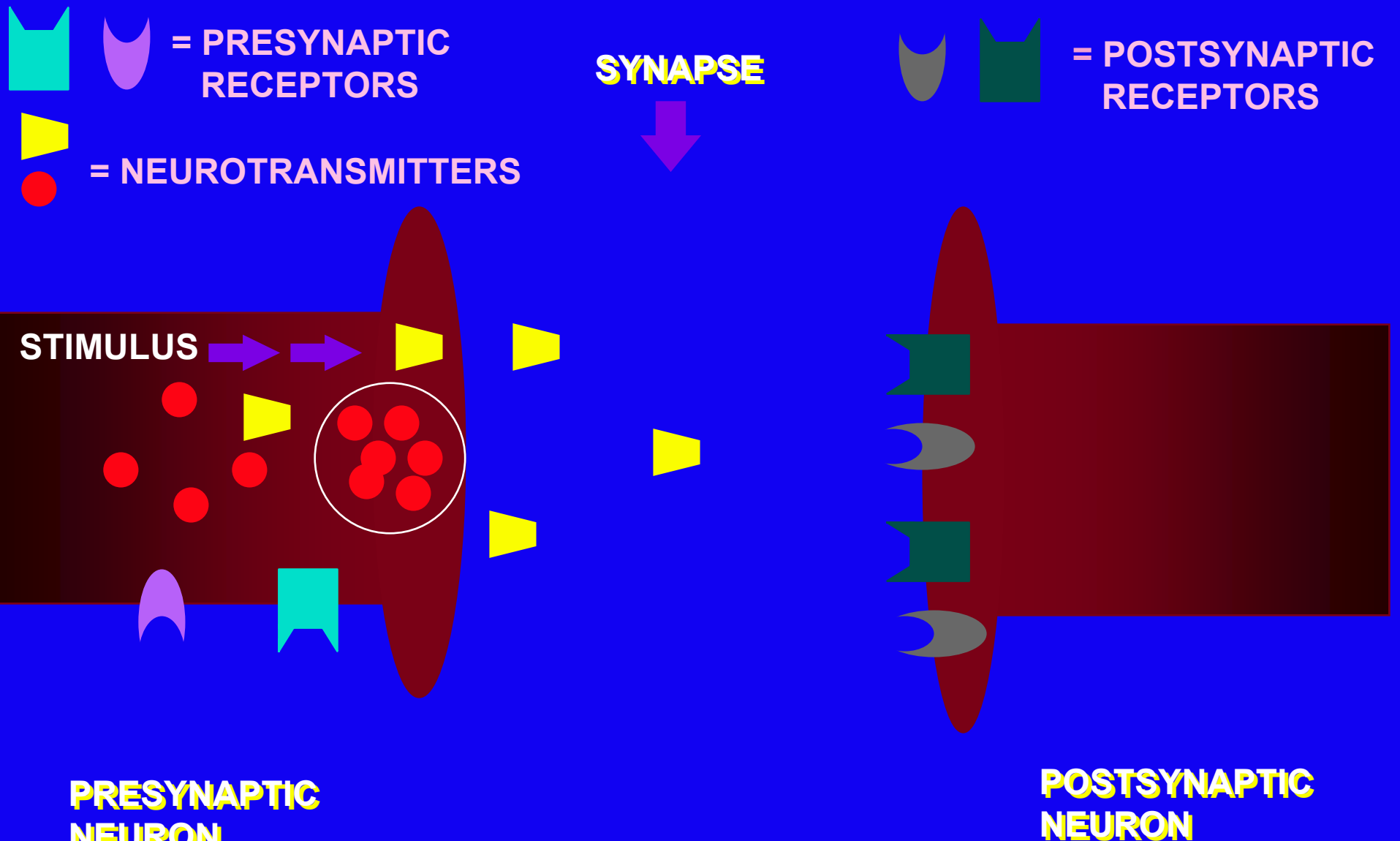
= VESICLES

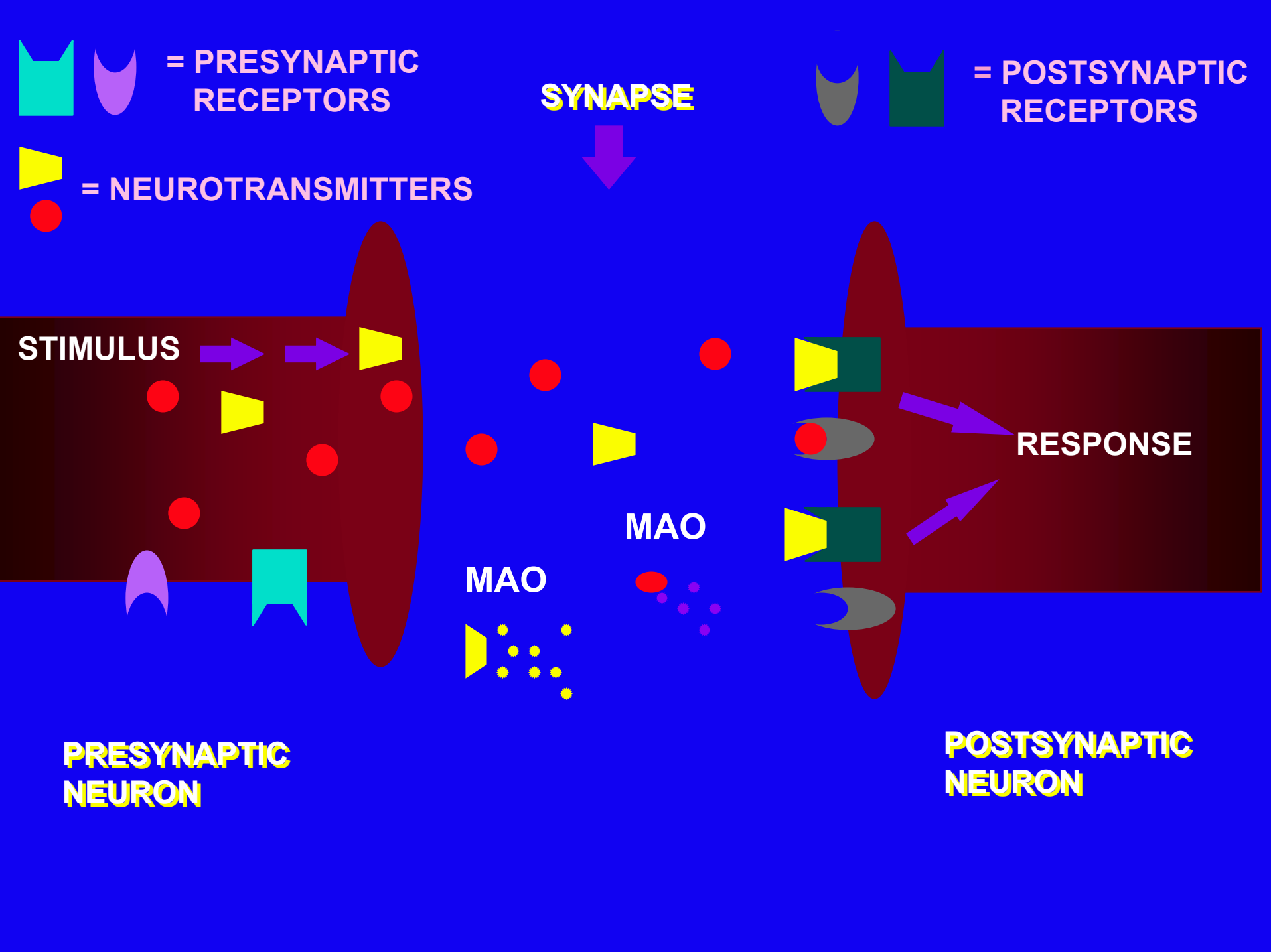


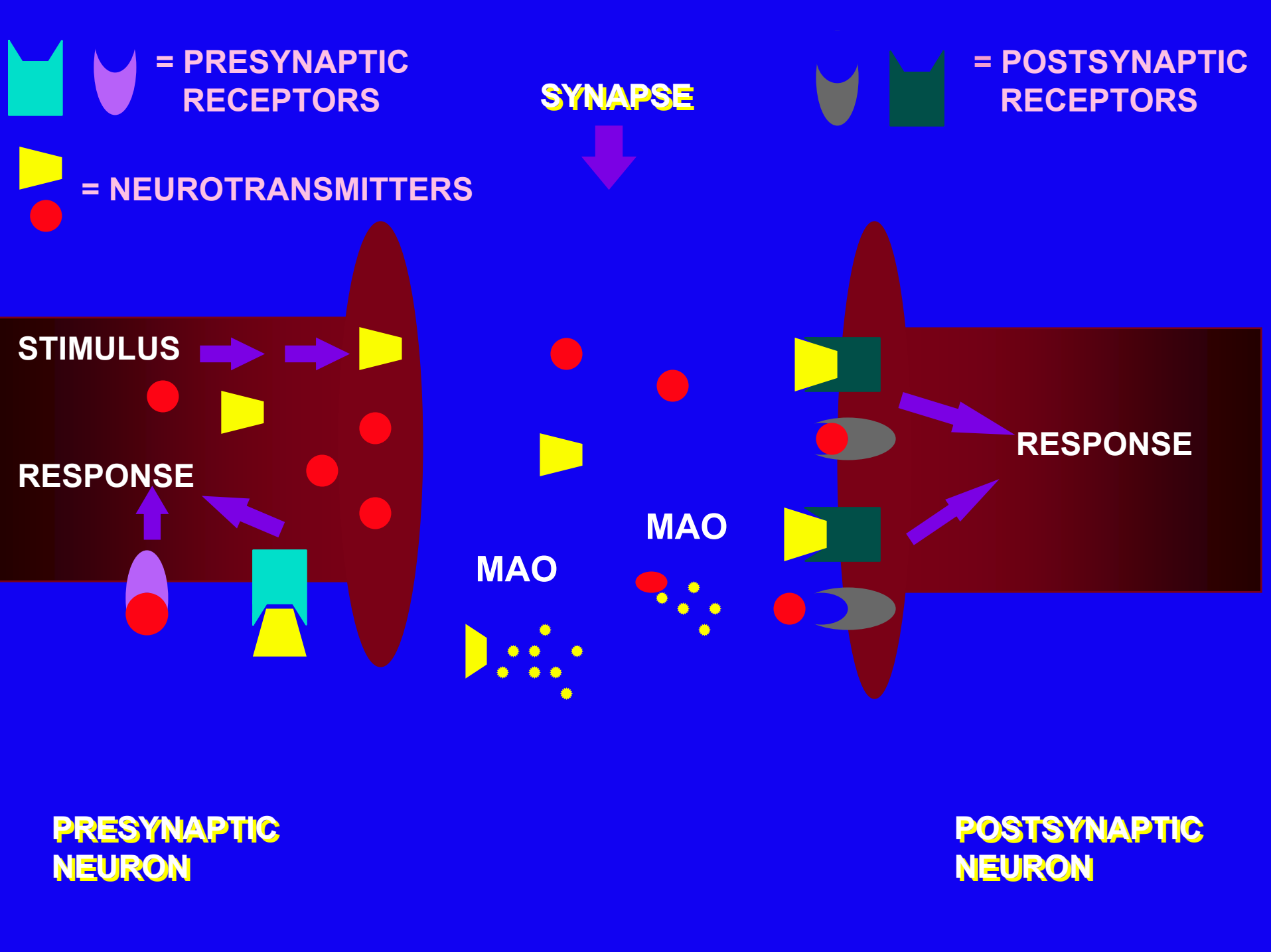


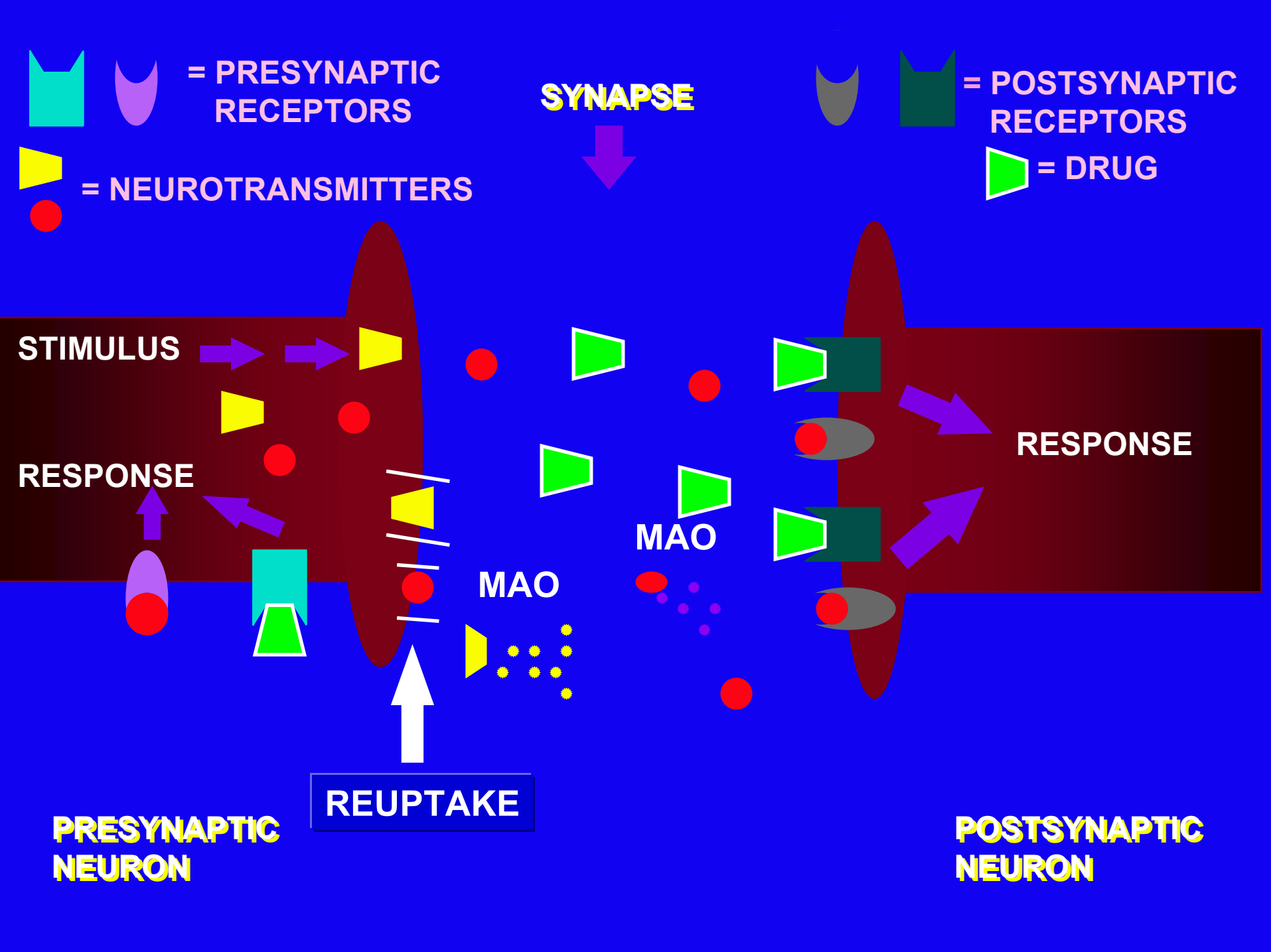
PRESYNAPTIC NEURON

POSTSYNAPTIC NEURON


= PRESYNAPTIC RECEPTORS
= NEUROTRANSMITTERS
SYNAPSE
= POSTSYNAPTIC RECEPTORS
STIMULUS
PRESYNAPTIC NEURON
POSTSYNAPTIC NEURON


= PRESYNAPTIC RECEPTORS
SYNAPSE
= POSTSYNAPTIC RECEPTORS
= NEUROTRANSMITTERS
STIMULUS
RESPONSE
MAO
MAO
PRESYNAPTIC NEURON
POSTSYNAPTIC NEURON


= PRESYNAPTIC RECEPTORS
SYNAPSE
= POSTSYNAPTIC RECEPTORS
= NEUROTRANSMITTERS
STIMULUS
RESPONSE
MAO
MAO
RESPONSE
PRESYNAPTIC NEURON
POSTSYNAPTIC NEURON


= PRESYNAPTIC RECEPTORS
SYNAPSE
= POSTSYNAPTIC RECEPTORS
= NEUROTRANSMITTERS
= DRUG
STIMULUS
RESPONSE
MAO
MAO
RESPONSE
REUPTAKE
PRESYNAPTIC NEURON
POSTSYNAPTIC NEURON

A Better Understanding of the "Reuptake Pump"

Delayed disinhibition of serotonin neurotransmission or reuptake pump inhibition:

(1) Increased serotonin in the somatodendritic area

(2) Serotonin 1-A autoreceptor desensitization

(3) Disinhibit or restore neuronal impulse flow

(4) Desensitization of postsynaptic serotonin receptors

Site of Action: Midbrain Raphe to Prefrontal Cortex

Symptom Remission

First Week

- Decreased Anxiety
- Improvement in Sleep
- Improvement in Appetite

1-3 Weeks

- Increased Activity, Sex Drive, Self-care, and Memory
- Thinking and Movements Normalize
- Sleeping and Eating Patterns Normalize

2-4 Weeks

- Relief of Depressed Mood
- Less Hopeless/ Helpless
- Thoughts of Suicide Subside

Kinetic Considerations

- **Metabolism**
  faster rate of absorption and peak hepatic function (>15 y.o. = adult)
- **Elimination**
  larger liver to body mass ratio

TCA's in Children

- Hydroxy metabolites associated with cardiac toxicity
- Children less adipose tissue, less of a "buffer" for concentration changes
- Decreased protein binding
- Divided doses to help prevent toxicity
- More rapid renal elimination
- Open label trials of TCA's showed better results than double-blind placebo controlled

SSRI's in Children

- **Dose - plasma concentrations**

  paroxetine and fluoxetine inhibit own metabolism
- **Dose - response curve**

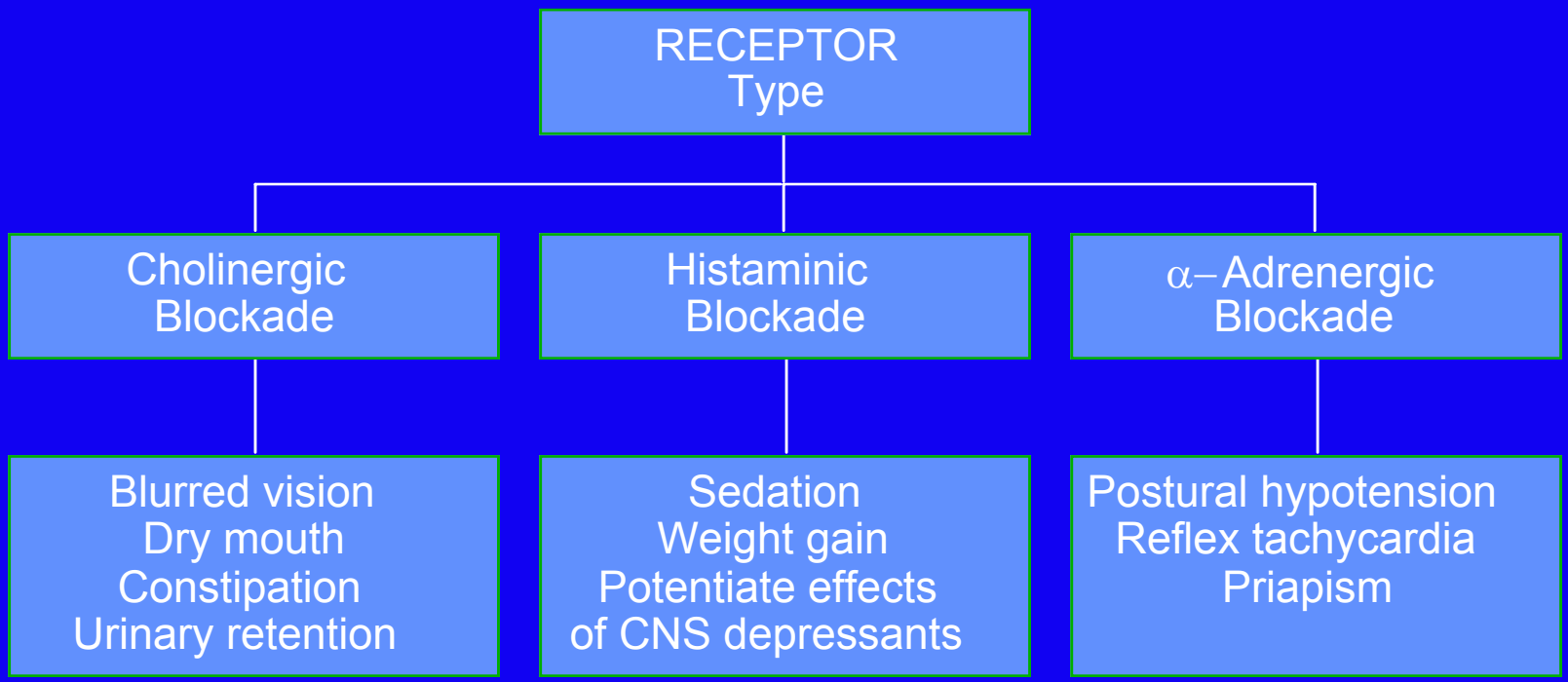
  flat dose-response
- **Metabolism and CYP450**

  substrates

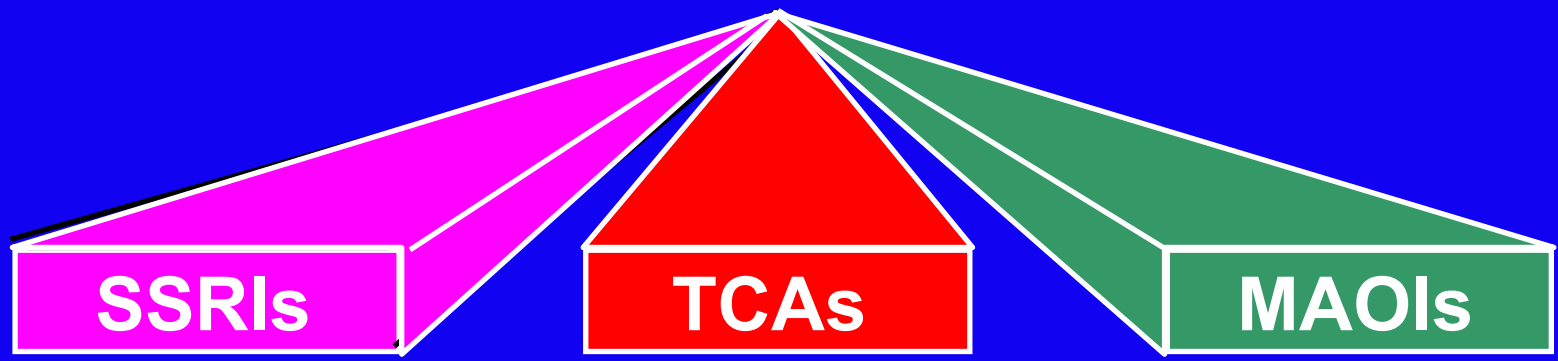
  inhibitors

  genetic polymorphism
- **Overdose and Toxicity**

Adverse Effects and Receptor Blockade



Antidepressant Side Effects

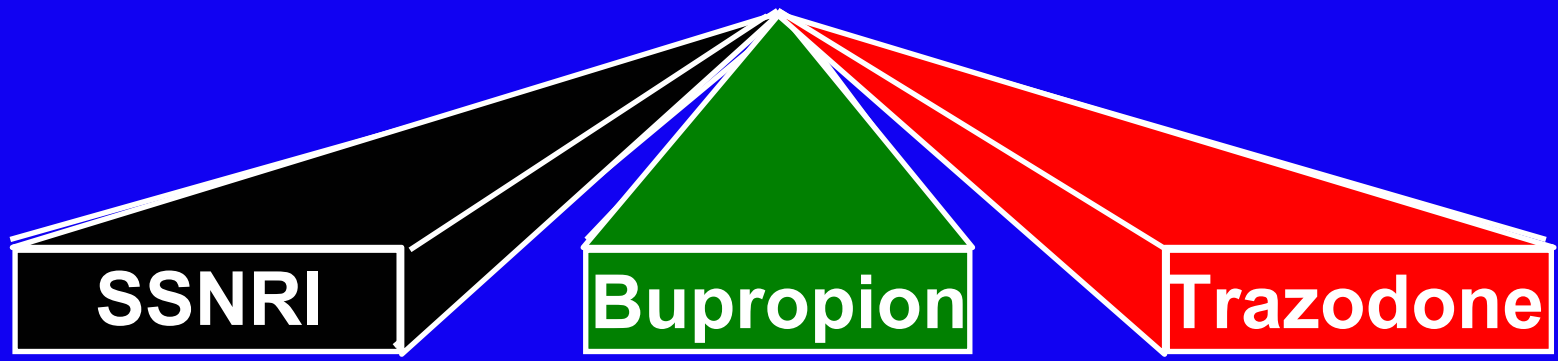


- Nausea
- Diarrhea
- Headache
- Nervousness
- Insomnia
- Sexual Dysfunction

- Drowsiness
- Dry Mouth
- Blurred Vision
- Constipation
- Hypotension
- Weight Gain
- Cardiac Effects
- Urinary Retention
- Sexual Dysfunction
- Memory Impairment

- Hypotension
- Dizziness
- Weight Gain
- Insomnia
- Cardiac Effects
- Constipation
- Sexual Dysfunction
- Palpitations
- Hypertensive Crisis

Antidepressant Side Effects

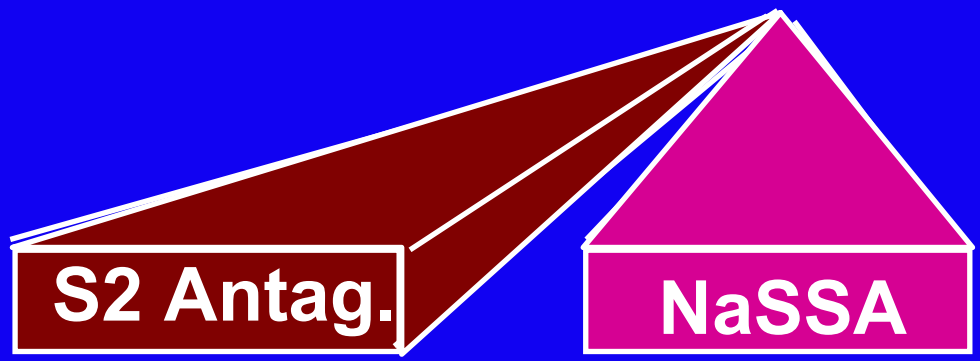


- Nausea
- Diarrhea
- Headache
- Hypertension
- Nervousness
- Insomnia
- Sexual Dysfunction

- Insomnia
- Seizures
- Weight Gain
- Cardiac Effects

- Hypotension
- Dizziness
- Weight Gain
- Constipation
- Sexual Dysfunction
- Memory Impairment

Antidepressant Side Effects



- constipation
- lightheadedness
- postural hypotension
- headache
- dry mouth
- nausea
- somnolence
- confusion
- visual changes
- sexual dysfunction

- sedation
- nausea
- weight gain
- dizziness
- dry mouth
- constipation
- visual changes
- pruitis/rash
- sexual dysfunction
- agranulocytosis

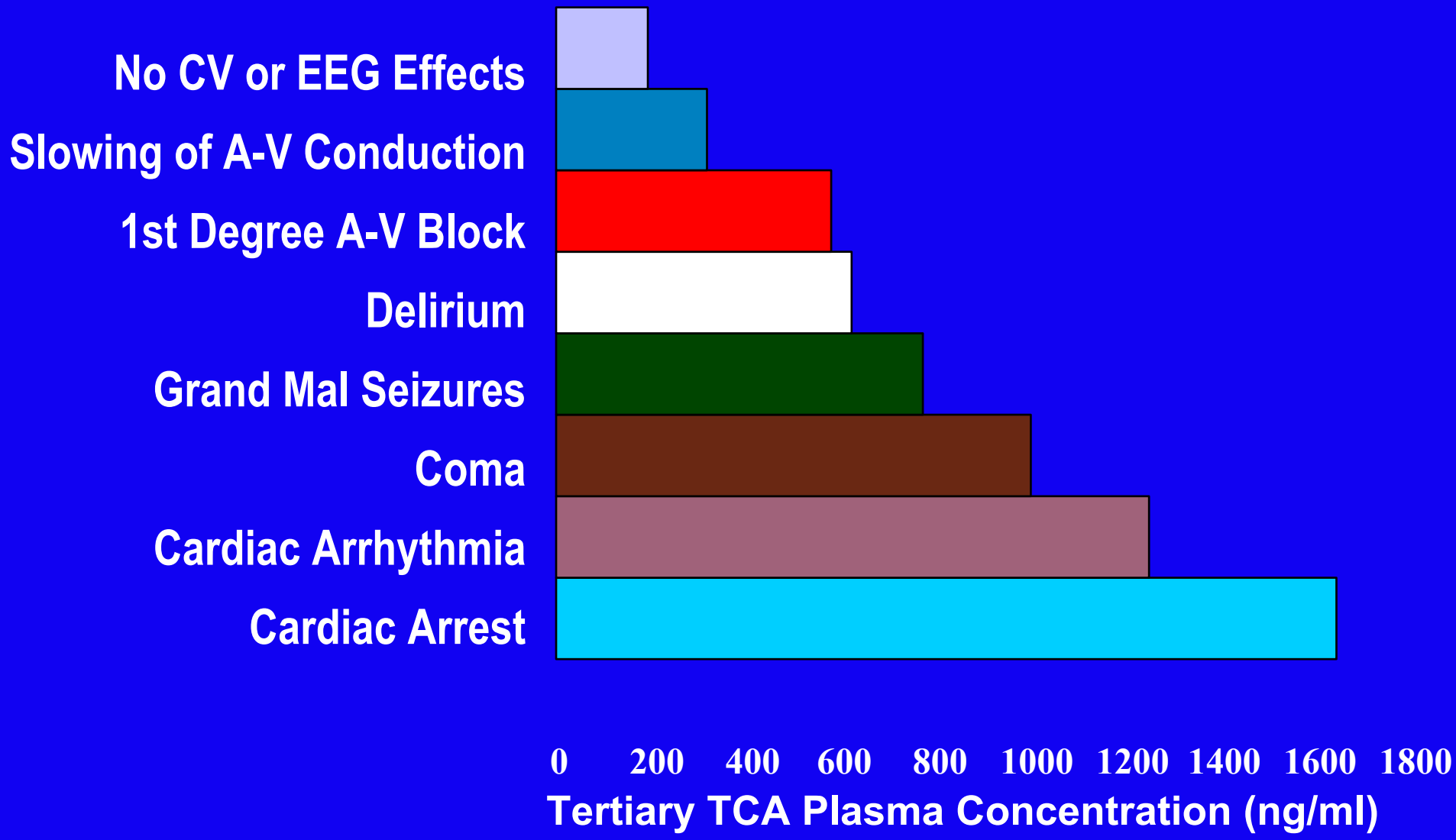
General Overview

- cardiac
- seizures
- weight changes
- sedation/insomnia
- sexual dysfunction

Cardiac

- orthostasis greatest with TCA's, MAOI's and trazodone
- heart block with TCA's
- hypertension with venlefaxine
- widening of QRS predictor of toxicity in OD with TCA's

TCA Concentrations and Toxicity



Preskorn SH, Fast GA. J Clin Psychiatry 1991;52(6):23-33

Seizures

- greatest concern with bupropion when dosed improperly
- TCA' especially in overdose
- drug interactions can be a cause

Weight Changes

- weight gain is greatest problem with TCA's, mirtazapine and MAOI's
- SSRI's can "normalize" weight gain from disese or drugs to baseline
- watch elderly for weight loss from SSRI's

Sedation

- Can be an advantage or a disadvantage
- Tolerance usually develops
- TCA's, nefazodone, mirtazapine biggest problem

Insomnia/Agitation

- SSRI's, bupropion and MAOI's are biggest problem

Insomnia and Agitation

- Is the cause the antidepressant or the depression ?
- Assess sleep quality and/or presence of agitation at baseline
- Is there another cause for the symptoms besides the depression or the antidepressant?
- concurent anxiety disorder
- medical problems
- medications

Treatment of Antidepressant-Induced Insomnia and Agitation

- good baseline assessment to ID cause
- tolerance may develop
- am dosing
- dose reductions
- temporary addition of hypnotic
- switch to more sedating drug

Sexual Dysfunction

- SSRI's are biggest problem
- can occur with all drugs
- disease or drug??

Assessment of Sexual Dysfunction

- Was sexual dysfunction was present at baseline?
- What is the specific problem?
- Has it changed with the addition of an antidepressant?
- Are there other diseases or factors that could cause or contribute to the dysfunction?
- Is the patient at risk for noncompliance?

Treatment of Antidepressant-Induced Sexual Dysfunction

- continue current treatment and observe for tolerance
- dose reduction or discontinuation if possible
- adjunctive medications (eg. yohimbine, cyproheptadine)
- switch to buproprion or nefazodone

Considerations for Adverse Effect Monitoring

- Is adverse effect acute or chronic in onset?
- Is tolerance to the adverse effect likely to develop with time?
- Has the patient been warned about the common adverse effects?
- Does the patient have a strategy to deal with an emerging adverse effect?

Other Adverse Effect Issues

- ***withdrawal*** **is a problem with:**
  - **highly serotonergic drugs**
  - **highly anticholinergic drugs**
- ***switching*** **is a problem with:**
  - **MAOI's**
  - **SSRI's and newer agents**
  - **manage with washout**

Serotonin Syndrome

Gastrointestinal

- abdominal cramping
- bloating
- diarrhea

Neurological

- tremor
- myoclonus
- dysarthria
- hyperreflexia
- restlessness

Cardiovascular

- tachycardia
- hypertension

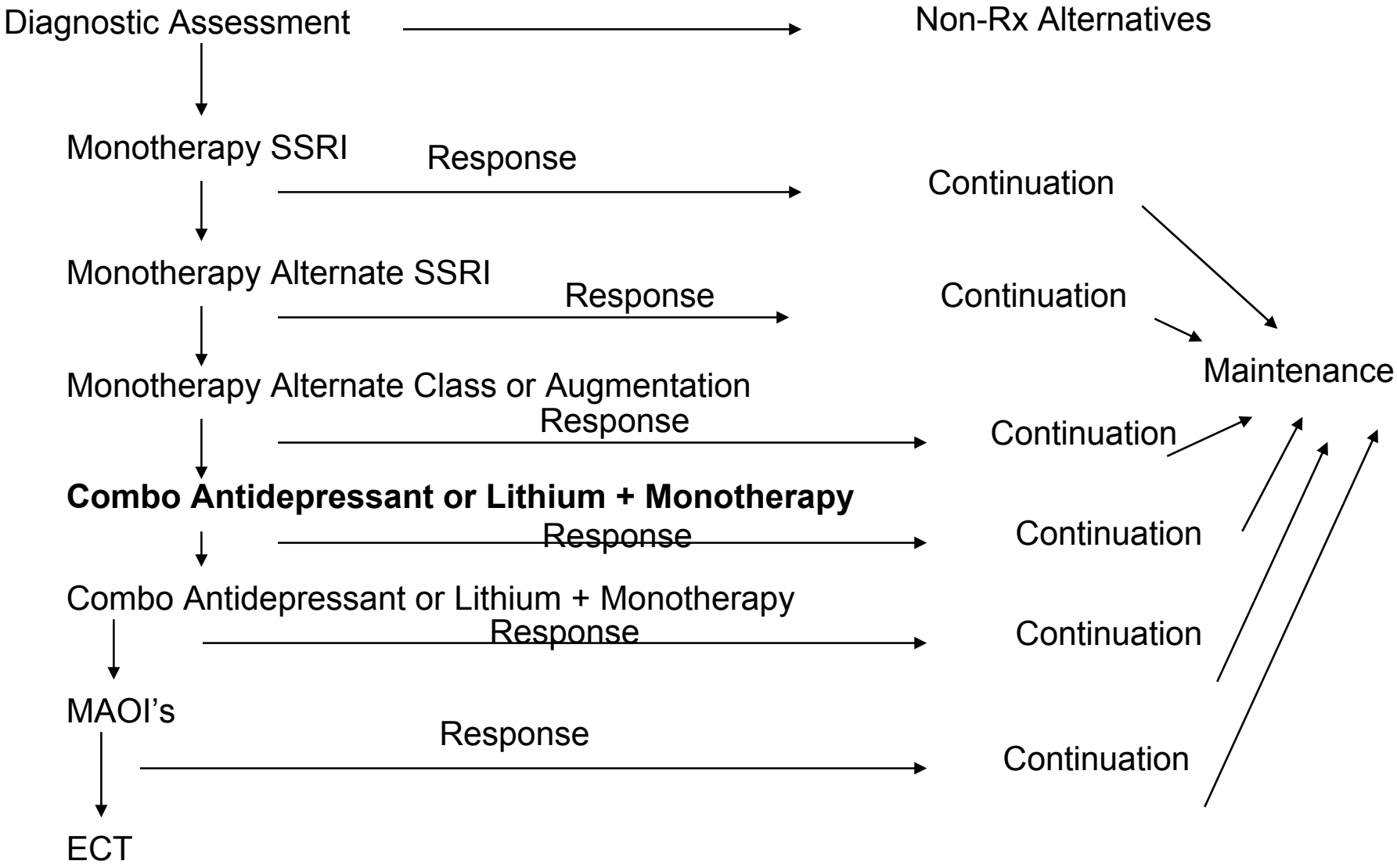
Psychiatric

- mania-like symptoms
- confusion

Other

- sweating

TMAP Algorithm for Childhood Major Depression



J Am Acad Child Adolesc Psychiatry, 38:11, November 1999.

Tricyclic Dosing Guidelines in Children

Amitriptyline:	**Start 0.5 mg/kg/day;**
	Range is 2-5 mg/kg
Nortriptyline:	**Start 0.5 mg/kg/day;**
	Range 1-3 mg/kg
Imipramine:	**Start 0.5 mg/kg/day;**
	Range 2-5 mg/kg
Desipramine:	**Start 0.5 mg/kg/day;**
	Range 2-5 mg/kg

Essent Psychopharmacol 1:4, April 1997.

SSRI Dosing in Children

Fluoxetine:	**Starting Dose**	**5-10 mg**
	Range	**10-40 mg**
Fluvoxamine:	**Starting Dose**	**25-50 mg**
	Range	**25-200 mg**
Paroxetine:	**Starting Dose**	**10-20 mg**
	Range	**10-50 mg**
Sertraline:	**Starting Dose**	**25-50 mg**
	Range	**25-200 mg**

Dosing Range (Adults)

Drug	Starting Dose (mg/day)	Usual Dose (mg/day)	Range (mg/day)
amitriptyline	25-50	100-300	75-300
trazodone	50	75-300	300-600
bupropion	150	300	150-450
phenelzine	15	15-90	15-90
mirtazapine	15	15-45	15-45
nortriptyline	25	50-200	50-200
imipramine	25-50	100-300	75-300

Dosing Range (Adults)

Drug	Starting Dose (mg/day)	Usual Dose (mg/day)
citalopram	20	20-60
fluoxetine	20	20-60
paroxetine	20	20-60
sertraline	50	50-200
venlafaxine	37.5	75-225
nefazodone	50	150-300

Antidepressant Kinetics

SSRI Pharmacokinetics

Kinetic Parameter	Citalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
T 1/2	33 hours	1-4 days (7-15 days for metab.)	17-22 hours	24 hours	24 hours
Clinical activity of metabolite ?	No	Yes	No	No	Yes
Auto-inhibition properties ?	No	Yes	Yes	Yes	No
Linear PK properties ?	Yes	No	No	No	Yes
Age-related PK changes ?	Yes	NA	No	Yes	No

Clinical Pharmacokinetics, 1997; 32 Suppl 1.

Effects on Cytochrome P450 Metabolic Pathways

+-Enzyme	Citalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
CYP1A2	Not Suspected	Not Suspected	>150% ↑ AUC	Not Suspected	Not Suspected
CYP2D6	20–50% ↑ AUC	>150% ↑ AUC	Not Suspected	>150% ↑ AUC	20-50 % ↑ AUC
CYP3A4	Not Suspected	20–50% ↑ AUC	50-100% ↑ AUC	Not Suspected	Not Suspected
CYP2C9	NA	NA	NA	Not Suspected	Not Suspected
CYP2C19	NA	50-100% ↑ AUC	>150% ↑ AUC	NA	Not Suspected

Clinical Pharmacokinetics, 1997; 32 Suppl 1.

CYP450 Degrees of Inhibition

Inhibition Potency	CYP2D6	CYP3A4	CYP1A2	CYP2C9	CYP2C19
High	Fluoxetine Paroxetine	Fluvoxamine Nefazodone	Fluvoxamine	Fluoxetine Fluvoxamine	Fluvoxamine
Moderate to Low	Sertraline	Fluoxetine			Fluoxetine
Low to Minimal	Venlafaxine Fluvoxamine	Sertraline Paroxetine Venlafaxine Citalopram	Fluoxetine Nefazodone Paroxetine Sertraline Citalopram		Venlafaxine
Not Known	Nefazodone Escitalopram	Escitalopram	Venlafaxine Escitalopram	Nefazodone Paroxetine Sertraline Venlafaxine Escitalpram	Nefazodone Paroxetine Sertraline Escitalopram

Drug Interactions

- kinetic
  - can cause or be affected by many agents
- dynamic:
  - anticholinergic
  - sedation
  - serotonin syndrome

CYP450 Systems

2D6

Substrates:

antipsychotics
beta blockers
1C antiarrythmics
TCA's
opiates
paroxetine

Inhibitors:

SSRI's (except fluvox)
quinidine

3A4

Substrates:

alprazolam, triazolam, quinidine,erythromycin, astemizole,terfenadine, carbamazepine,TCA's, sertraline, citalopram

Inhibitors:

ketoconazle
nefazodone, sertraline, fluoxetine

CYP450 Systems

1A2

Substrates:

theophylline
warfarin
TCA's
caffeine

Inhibitor:

fluvoxamine

Inducer:

smoking, BBQ
rifampin
omeprazole

2C

Substrates:

diazepam, TCA's
propranolol
warfarin
tolbutamide
phenytoin
citalopram

Inhibitor:

fluoxetine,
fluvoxamine, sertraline

Inducer:

phenobarbital ethanol

Antidepressant TDM

- Generally useful when
  - larger doses are given and there is a lack of therapeuticy cardiac toxicity
  - in children - primarily for toxicity and dosing

Antidepressant TDM

- Sampling is usually done in the morning prior to any AM doses of drug
- Cpss reached in 5-7 days after dosage adjustments
- Most data with TCAs
- TDM usually not needed in patients with TCA doses ≤ 150 mg/day, with out significant medical illness, and who are responding in 2-3 weeks

Antidepressant TDM

Drug	Range (ng/ml)
Amitriptyline (Elavil)	12 - 250 (ami + nor)
Desipramine (Norpramin)	115 - 250
Imipramine (Tofranil)	180 - 350 (imi + dmi)
Nortriptyline (Pamelor)	50 - 150
Trazodone (Desyrel)	750 - 1500
MAOIs (Nardil, Parnate)	N/A
SSRIs (Prozac, Paxil, Zoloft)	N/A
Bupropion (Wellbutrin)	50 - 100

Dosing Problems

- one dose fits all versus dose flexibility
- inappropriate dose increases
- inappropriate dose reductions
- inadequate treatment duration
- undertreatment of some individuals

Antidepressant Comparisons

Not So Selective SSRI's ??

Clinical Implications of Secondary Pharmacologic Properties

- **Fluoxetine**
  - **5HT2C agonist**
- **Sertraline**
  - **Dopamine reuptake inhibition**
- **Paroxetine**
  - **Anticholinergic**
- **Fluvoxamine**
  - **Sigma receptor interaction**
- **Citalopram**
  - **Serotonin selectivity**

SSRI Selectivity

Escitalopram

Citalopram

Sertraline

Fluvoxamine

Fluoxetine

Paroxetine

Most Selective

Least Selective

SSRI's in Depression

Advantages

- **once daily dosing**
- **treats co-morbid anxiety**
- **no dependence**
- **side effects well tolerated**
- **reduced toxicity**

Disadvantages

- **delayed onset of action**
- **flat dose response curve**
- **more expensive than TCA's**
- **initial stimulation**

Tricyclic Antidepressants in Depression

Advantages

- **once daily dosing**
- **treats comorbid anxiety**
- **no dependence**

Disadvantages

- **delayed onset of action**
- **adverse effects**
- **overdose**
- **initial stimulation**

MAOI's in the Treatment of Depression

Advantages

- **tolerated as well or better than TCA**
- **treats co-morbid anxiety**
- **no dependence**
- **positive results with agoraphobia**

Disadvantages

- **delayed onset of action**
- **hypertensive crisis and dietary restriction**
- **initial stimulation**
- **weight gain**
- **sexual dysfunction**

Childhood Bipolar Disorder

Childhood Bipolar Disorder

- 20% of all bipolar patients have symptoms before the age of 20
- Similar child vs. adult presentation
- Early onset < 18 yo
- Very early onset < 13 yo
- 20 - 30% with major depression will develop manic symptoms
- Mania often noted as change in mood, increased agitation, labile, and erratic vs. being euphoric
- Onset before the age of 10 yo < 0.5%
- Differential diagnosis (e.g. schizophrenia)

Bipolar Disorder - Manic

- **A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week.**
- **During the disturbance, three or more of the following symptoms have persisted (4 if mood only irritable):**

- Inflated self-esteem or grandiosity
- Decreased need for sleep
- Hypertalkative / Pressured Speech
- Flight of ideas or racing thoughts
- Easily distracted
- Increase in goal directed activity / psychomotor agitation
- Increased involvement in pleasurable activities with potentially painful consequences

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, 2000.

Bipolar Disorder Goals of Therapy

1) Amelioration of Acute Symptoms

2) Prevention of Relapse

3) Reduction of long-term morbidity

4) Promotion of long-term growth and development

Mood Stabilizer Pharmacologic Management of Bipolar Disorder

Lithium carbonate immediate release (Lithotab®)

Lithium carbonate extended release (Lithobid®, Eskalith®)

Lithium citrate

Valproic acid (Depakote®, Depakene®)

Carbamazepine (Tegretol®, Tegretol XR®)

Investigational

Lamotrigine

Gabapentin

American Psychiatric Association Practice Guidelines, 1994.
AACAP Practice Parameters. *J Am Acad Child Adolesc Psychiatry* 1997; 36(1).
Sachs GS. J Clin Psychopharmacol, 1996.
Kowatch RA. *J Am Acad Child Adolesc Psychiatry* 2000; 39(6).
Donovan SJ. *Am J Psychiatry* 2000; 157(5).

Additional Treatments for Bipolar Disorder

- Benzodiazepines
- Antidepressants
- Antipsychotics
- Propranolol
- Calcium channel blockers
- Adrenergic agonists
- Propranolol
- Electroconvulsive treatment (ECT)

Mood Stabilizers in Children

Lithium Carbonate

Started 300-900 mg/day (Approx 30/mg/kg/day)

Therapeutic Range 0.6 - 1.2 mEq/L

Valproic Acid

Started 10-60 mg/kg/day (1,000 - 3,000 mg/day)

Therapeutic Range 50 - 120 mg/L

Carbamazepine

Started 100 - 300 mg/day

Therapuetic Range 4 - 12 mg/L

Gabapentin

LITHIUM MECHANISM

- Altered ion channel permeability
- Acute increased norepinephrine turnover
- Chronic administration increases dopamine turnover in striatal and mesolimbic areas
- Blocks dopamine receptor supersensitivity
- Serotonin agonist

Adapted from:
Jefferson JW, et al. Lithium Encyclopedia for Clinical Practice (Second Edition), 1987.

BASELINE MEASURES FOR INITIATION OF LITHIUM CARBONATE

- General history
- Physical exam
- BUN
- Renal function
  - every 2 months for first 6 months, then every 6 months to year
- Thyroid function
  - once in first 6 months, then once every 6 months to year
- CBC with differential
- Serum pregnancy test
- EKG if over 40 years
- Serum concentration
  - monitor 5 days after dose adjustment and every 6 months while stable

American Psychiatric Association Practice Guidelines, 1994.

LITHIUM SIDE EFFECTS
Dose Related

- Polyuria
- Polydypsia
- Weight gain
- Cognitive problems
- Tremor
- Sedation
- Lethargy
- Impaired coordination
- GI upset
- Hair loss
- Leukocytosis
- Acne
- Edema

American Psychiatric Association Practice Guidelines, 1994.

MILD LITHIUM TOXICITY

Concentrations 1.5-2.0 mEq/L:

Lethargy
Drowsiness
Coarse hand tremor
Muscular weakness

Nausea
Vomiting
Diarrhea

Finley PR, et al. *Clin. Pharmacokinet* 1995; 29: 172-191.

MODERATE LITHIUM TOXICITY

Serum concentrations between 2.0 - 2.5 mEq/L:

- Confusion
- Dysarthria
- Nystagmus
- Ataxia
- Myoclonic twitches
- ECG changes (flattened T wave)

Finley PR, et al. Clin. Pharmacokinet 1995; 29: 172-191.

SEVERE LITHIUM TOXICITY

Serum concentrations > 2.5 meq/L:

- **Impaired consciousness**
- **Increased deep tendon reflexes**
- **Seizures**
- **Syncope**
- **Renal insufficiency**
- **Coma**
- **Death**

Finley PR, et al. *Clin. Pharmacokinet* 1995; 29: 172-191.

POTENTIAL LITHIUM DRUG INTERACTIONS

Sodium deficiency
increased lithium levels

Thiazide diuretics
increased lithium levels

NSAID's
increased lithium levels

ACE inhibitors
increased lithium levels

Antipsychotics
increased neurotoxicity

Calcium channel blockers
increased lithium levels

Theophylline/Caffeine
decreased lithium levels

Finley PR, et al. Clin Pharmacokinet, 1995.

VALPROATE MECHANISM

- Inhibits GABA transaminase and succinic semi-aldehyde dehydrogenase catabolism of GABA
- Increased brain GABA content
- Enhanced postsynaptic GABA effects
- Activates GABA synthesis

Post RM. J Clin Psychiaty, 1989.
Fawcett J. J Clin Psychiatry, 1989.

VALPROATE MONITORING

- General medical history
- Chemistry profile
  - baseline and every 6 months
- Pregnancy test
- Serum concentration
  - maintain 45-125 mcg/ml
- CBC with differential
  - baseline and every 6 moths
- Liver function tests
  - baseline and every 6 months

American Psyciatric Association Practice Guidelines, 1994.

VALPROATE SIDE EFFECTS

DOSE RELATED

Benign increase in LFT's

Tremor

Sedation

Alopecia (usually transient)

GI upset (anorexia, nausea, vomiting, diarrhea)

Leukopenia / Thrombocytopenia

Increased appetite

Weight gain

American Psychiatric Association Practice Guidelines, 1994.

VALPROATE SIDE EFFECTS

IDIOSYNCRATIC

Polycystic ovaries

Hyperandrogenism

Hepatic failure (do not use in children < 2) [a]

Pancreatitis (mentally retarded)[b]

Agranulocytosis

American Psychiatric Association Practice Guidelines, 1994.

[a] Pellock JM. Neurology, 1991.

[b] Buzar AD, et al. J Clin Psychiatry, 1995.

VALPROATE DRUG INTERACTIONS

Hepatically metabolized drugs

increased serum concentraions

Protein bound drugs

increased effects of warfarin and aspitin

Phenytoin

increased free concetrations of phenytoin

Carbamazepine

increased free carbamazepine and epolxide levels

SSRI's

increased valproate concentrations

McEvoy G. AHFS Drug Information, 1993.

CARBAMAZEPINE MECHANISM

Kindling at amydala

Alpha-2 adrenergic stimulation

Potentiation of $GABA_B$

Sodium channel stabilization

Post RM. j Clin Psychiatry, 1989.

Carbamazepine Monitoring Parameters

- **General medical history and physical exam**

  baseline with emphasis on history of dyscrasias or liver disease
- **CBC with differential and platelet count**

  every 2 weeks in first 2 months of treatment and then every 3 months if normal
- **Liver function test**

  every 2 weeks in first 2 months of treatment and then every 3 months if normal
- **Renal function test**
- **Serum electrolytes**
- **Serum concentrations**

  5 days after dosage changes until stable

American Psychiatric Association Practice Guidelines, 1994.

CARBAMAZEPINE SIDE EFFECTS
DOSE RELATED

Diplopia
Blurred vision
Fatigue
Nausea
Ataxia

Skin rash
Leukopenia
Thrombocytopenia
Hyponatremia (6%-31%)
LFT increases (5%-15%)

American Psychiatric Association Practice Guidelines, 1994.

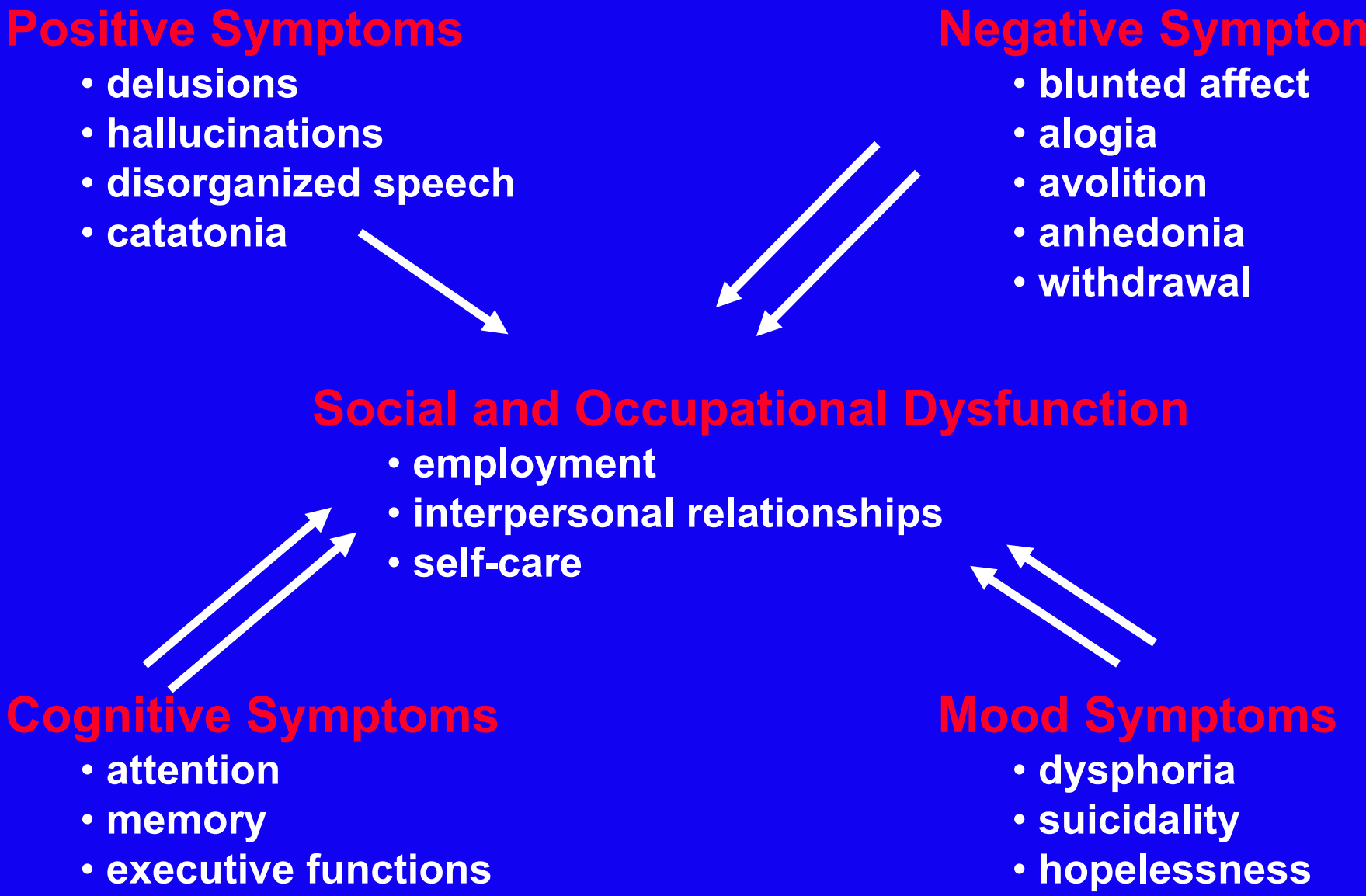
CARBAMAZEPINE SIDE EFFECTS
IDIOSYNCRATIC

- **Agranulocytosis**
- **Aplastic anemia**
- **Hepatic failure**
- **Exofoliative dermatitis (e.g. Stevens-Johnson Syndrome)**
- **Pancreatitis**

American Psychiatric Association Practice Guidelines, 1994.

Childhood Schizophrenia

Schizophrenia: Core Symptom Clusters



Schizophrenia in Children

- **Associated Clinical Features**
  - Rarely occurs before the age of 12 yo
  - Rate increases in adolesence (0.1% / yr)
  - Youngest reported onset at 3 yo
  - Early onset more common in males (2:1)

  (30% of adult schizophrenia patients presented with symptoms < 18 yo)
  - Both acute and insidious onset reported
  - Second trimester development involved
  - 10-20% of early onset have low IQ scores

AACAP Practice Parameters for Children and Adolescents with Schizophrenia

- Diagnostic Assessment
- Diagnostic Formulation

  differential diagnosis
- Treatment

  acute

  recovery

  residual and remission

  psychosocial therapy

AACAP Practice Parameters. *J Am Acad Child Adolesc Psychiatry* 1997; 36(10).

Antipsychotics in Children

- Schizophrenia
- Mood Disorders
- Autism
- Mental Retardation
- Tourette's Disorder
- Conduct Disorder
- Oppositional Defiant Disorder
- Anorexia Nervosa
- Attention Deficit Hyperactivity Disorder
- Personality Disorder

Serotonin and Dopamine in Schizophrenia

- Serotonin activity in dorsal raphe
  - inhibit DA neurons in substantia nigra
  - inhibits DA synthesis/release in cortex and striatum
- Dopamine inhibition and EPS
  - enhanced by 5-HT precursors, SSRIs
  - decreased by 5-HT2 antagonists, 5-HT1 agonists

Disadvantages of Conventional Antipsychotics

- 20% - 40% nonresponse
- Positive symptoms respond more than negative symptoms
- 35% relapse rate in schizophrenia
- Developed on basis of DA hypothesis
- Sedation
- Anticholinergic effects
- EPS
- Seizures

Atypical Antipsychotic Agents

"Atypical" because:

- lower potential for extrapyramidal effects
- greater efficacy in negative symptoms
- greater efficacy in refractory illness
- lower potential to cause prolactin elevations
- greater 5HT-2/D2 receptor effects

Antipsychotic Dosing in Children and Adolescents

Chlorpromazine	10-200 mg/day (600)
Thioridazine	10-200 mg/day (600)
Haloperidol	0.25-6 mg/day (16)
Pimozide	1-6 mg/day (NTE 30 mg/day)
Loxapine	25-200 mg/day
Clozapine	100-700 mg/day
Olanzapine	2.5-15 mg/day (20)
Risperidone	0.5-4 mg/day (6)

Conduct Disorder

Conduct Disorder

A repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated, as manifested by the presence of 3 or more of the following in the past 12 months, with at least one criteria present in the past 6 months:

American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), 2000.

Conduct Disorder

Aggression to people and animals

bullies, initiates fights, used weapon, physically cruel to people, physically cruel to animals, stolen, forced someone into sexual activity

Destruction of property

fire setting, destruction of property

Deceitfulness or theft

broken in house, building, car; lies to obtain goods or favors or to avoid obligations; shoplifting

Serious violations of rules

stays out at night despite parental prohibitions; run away from home; truant from school

American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), 2000.

Conduct Disorder

More often associated with males (5:1)
Overall prevalence approximately 3% (1.5% to 3.4%)
May account for as much as 30-50% of all childhood referrals

Childhood onset type - criteria present prior to age 10
Adolescent onset type - absence of criteria prior to age 10

Mild – only minor harm caused to others
Moderate – “mild” to “severe”
Severe – result in considerable harm to others

Conduct Disorder Risk Factors

- Genetic Link - Familial Prevalence
- Neglect and Abuse
- Neurochemical Imbalance
  - dopamine, norepinephrin, serotonin
- Gender-gap closes in adolescence
- Temperament-makes target for parental anger
- Hyperactive
- Chronically Ill - 3X increased risk
- Low Family Functioning - Environment

Oppositional Defiant Disorder

A pattern of negativistic, hostile, and defiant behavior lasting at least 6 months, during which 4 or more of the following are present:

- often loses temper
- actively defiant to rules
- blaming of others
- angry and resentful
- argues with adults
- deliberately annoying
- easily annoyed
- spiteful and vindictive

American Psychiatric Association, DSM-IV-TR, Washington DC, 2000.

Intermittent Explosive Disorder

- Several discrete episodes of failure to resist aggressive impulses that result in serious assaultive acts or destruction of property.
- The degree of aggressiveness expressed is grossly out of proportion to any precipitating psychosocial stressors.
- The aggressive episodes are not better accounted for by another mental disorder.

American Psychiatric Association, DSM-IV-TR, Washington DC, 2000.

AACAP Practice Parameters for Conduct Disorder

Diagnostic Assessment

- Patient History
- Family History
- Interview
- School Information
- Physical Exam
- Diagnostic Formulation

Treatment

- Comorbidity
- Family Intervention
- Psychotherapy
- Psychopharmacology
  - Antidepressants
  - Mood Stabilizers
  - Antipsychotics
  - Propranolol

J Am Acad Child Adolesc Psychiatry 1997; 36(10).

Conduct Disorder with Aggression - Treatments

Antipsychotics

haloperidol

risperidone

chlorpromazine

thioridazine

stelazine

Mood Stabilizers

lithium

valproic acid

carbamazepine

gabapentin

Antidepressants

nefazodone

trazodone

selective serotonin reuptake inhibitors

Propranolol

Nadolol

Buspar

Stimulants

Clonidine

Tourette's Disorder

Tourette's Disorder

Multiple motor and one or more vocal tics present at some time during the illness but not necessarily concurrently.

Tics occur many times a day nearly every day or intermittently throughout a period of more than 1 year, and during this period there was never a tic-free period of more than 3 consecutive months.

Disturbances caused marked distress or significant improvement in social, occupational, or other important areas of functioning.

Onset before the age of 18.

Tourette's Disorder

Epidemiology

- Estimated to affect 4-5 per 10,000 people
- Motor tics occur by age 7, vocal by age 11
- 3 x more common in males

Etiology

- Genetic - transferred in autosomal dominant gene
- Comorbidity - ADHD, OCD, CD
- Neurochemical - dopamine and norepinephrine
- Basal Ganglia and Frontal Cortex

Tourette's Treatments

Psychotherapy generally ineffective

**Haloperidol - most frequently prescribed and used in low doses (0.25 - 3 mg per day)

**Pimozide - dosed 1-2 mg per day in divided doses (cardiotoxicity issues)

Clonidine and Guanfacine - shown effective in comorbid Tourette's and ADHD

Risperidone - new literature supports decreasing tic frequency

** some evidence suggests pimozide efficacy > haloperidol efficacy

Mental Retardation

Mental Retardation and the Developmentally Disabled

Antipsychotics

- Risperidone

Antidepressants

- Fluoxetine
- Sertraline

Mood Stabilizers

- Valproic Acid
- Lithium
- Carbamazepine

Anxiolytics

- Buspirone
- NO BENZO IF POSSIBLE !
- Propranolol
- Naltrexone for SIB
- Stimulants

Side Effects in the Mentally Retarded Population

• Aminophylline	aggression
• Anticholinergics	cognitive impairment, delirium
• Carbamazepine	elevated epoxide, hyponatremia, folic acid deficiency
• Gabapentin	aggression
• Lithium	cognitive dulling, fluid intake
• Benzodiazepines	disinhibition, SIB
• Methylphenidate	tics, social withdrawal
• Antipsychotics	EPS (pseudopark, TD, akathisia
• Phenobarbital	irritability, SIB, aggression
• Phenytoin	intoxication
• Valproate	pancreatitis, hepatotoxicity

HCFA Regulations for Psychotropics in the Mentally Retarded

- Prior to prescribing medication
  - rule out environmental and medical behavior links
  - detailed description of symptoms and diagnostic formulation
  - collect behavioral data
  - utilize the least intrusive and most positive interventions

HCFA Regulations for Psychotropics in the Mentally Retarded

- When medication is prescribed
  - integral part of overall individual treatment plan
  - should not diminish functional status
  - utilize lowest effective dose
  - annual attempts at dose reduction
  - monitor adverse drug reactions
  - documentation of symptom response

Psychotropic Medications in Autistic Disorder

Steven C. Stoner, Pharm.D., BCPP
Clinical Associate Professor of Pharmacy Practice
UMKC School of Pharmacy
Northwest Missouri Psychiatric Rehabilitation Center

Pervasive Developmental Disorders

- Autistic Disorder
- **Rett's Disorder**
- **Childhood Disintigrative Disorder**
- **Asperger's Disorder**
- **PDD Not Otherwise Specified**

***Often associated with some degree of mental retardation**

Autistic Disorder

- 2 to 5 / 1,000 children affected
- Symptoms often present before 36 months
- Boys > Girls
- Special skills may be present
  - Calendar
  - Decoding
- Seizures present in 25% of cases

Etiology

- Psychodynamic and family factors
- Organic-neurological abnormalities
- Genetic factors
- Immunological factors
- Perinatal factors
- Neuranatomical findings
- Biochemical findings
  - Increased CSF homovanillic acid
  - Elevated plasma serotonin

Autistic Disorder

- **Qualitative impairment in social interaction, as manifested by at least two of the following:**
  - **Impaired use of multiple nonverbal behaviors**
  - **Failure to develop peer relationships appropriate to developmental level**
  - **Lack of spontaneous seeking to share enjoyment, interests, or achievements with other people**
  - **Lack of social or emotional reciprocity**

American Psychiatric Association, DSM-IV-TR, 2000.

Autistic Disorder

- **Qualitative impairments in communication as manifested by at least one of the following:**
  - **Delay in, or total lack of, the development of a spoken language**
  - **In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others**
  - **Stereotyped and repetitive use of language or idiosyncratic language**
  - **Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level**

American Psychiatric Association, DSM-IV-TR, 2000.

Autistic Disorder

- **Restricted repetitive and stereotyped patterns of behavior, interests, and activities as manifested by at least one of the following:**
  - **Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus**
  - **Apparently inflexible adherence to specific, nonfunctional routines or rituals**
  - **Stereotyped and repetitive motor mannerisms**
  - **Persistent preoccupation with parts or objects**

American Psychiatric Association, DSM-IV-TR, 2000.

Autistic Disorder

- **Delays or abnormal functioning in at least one of the following areas, with onset prior to the age of 3:**
  - **Social interaction**
  - **Language as used in social communication**
  - **Symbolic or imaginative play**

American Psychiatric Association, DSM-IV-TR, 2000.

Pharmacology Targeted Symptoms

- Aggression
- Self-injurious behavior
- Hyperactivity / Impulsivity
- Depression
- Inattention
- Anxiety / Obsession

GOAL = reduce behaviors to allow educational and behavioral treatments the opportunity to be effectve.

Neurochemical Basis

- Increased Serotonin
  - Whole-blood
  - Platelet
  - Increased platelet serotonin transport
  - Decreased central serotonergic responsivity
- Short-Term Tryptophan Depletion Studies
  - Autism studies worsen behavior
  - Depression / OCD / Panic do not worsen

Autism and Behavioral Control

Antipsychotics in Children

- Schizophrenia
- Mood Disorders
- Autism
- Mental Retardation
- Tourette's Disorder
- Conduct Disorder
- Oppositional Defiant Disorder
- Anorexia Nervosa
- Attention Deficit Hyperactivity Disorder
- Personality Disorder

Serotonin and Dopamine

- Serotonin activity in dorsal raphe
  - inhibit DA neurons in substantia nigra
  - inhibits DA synthesis/release in cortex and striatum
- Dopamine inhibition and EPS
  - enhanced by 5-HT precursors, SSRIs
  - decreased by 5-HT2 antagonists, 5-HT1 agonists

Disadvantages of Conventional Antipsychotics

- **20% - 40% nonresponse**
- **Positive symptoms respond more than negative symptoms**
- **35% relapse rate in schizophrenia**
- **Developed on basis of DA hypothesis**

Antipsychotic Side Effects

- Antihistaminergic Effects = Sedation
- Anticholinergic Effects = Constipation / Drying
- Dopamine Blockade
  - EPS
    - Dystonia
    - Pseudoparkinsonism
    - Akathisia
    - Tardive Dyskinesia
  - Elevations in prolactin
    - Osteoporosis potential
- Seizures

Atypical Antipsychotic Agents

"Atypical" because:

- lower potential for extrapyramidal effects
- greater efficacy in negative symptoms
- greater efficacy in refractory illness
- lower potential to cause prolactin elevations
- greater 5HT-2/D2 receptor effects

Risperidone in Autism with Mental Retardation

- **Case reports have shown decreased aggression, hyperactivity, and self-injury**
- **Dosed 3 to 4 mg per day**

Dartnall DA. Journal of Autism and Developmental Disoders, 1999: 29(1): 87-91.

Risperidone and Autism

- **Double-blind, placebo controlled trial (8 weeks)**
- **101 Children Enrolled (Risperidone = 49 / PBO = 52)**
- **Risperidone dosed 0.5 to 3.5 mg per day**
  - **56.9 % decrease in irritability (Aberrant Behavior Checklist)**
  - **69% had >25% decrease in irritability score and much improved or very much improved on CGI-I**
  - **Stereotypy and hyperactivity also improved**
  - **23 / 34 maintained response at 6 months**
  - **Side Effects: appetite increase, fatigue, drowsiness, dizziness, drooling**
  - **Risperidone Weight Gain = 2.7 kg**

McCracken JT, et al. The New England Journal of Medicine, 2002: 347(5): 314-321.

Risperidone in Adult Autistic Disorder

- **12-week, double-blind, placebo controlled**
- **N = 31 adults with autism and PDD NOS**
- **8 / 14 (57%) responded to risperidone**
  - **Repetitive behaviors**
  - **Aggression**
  - **Anxiety / nervousness**
  - **Depression**
  - **Irritability**
  - **Global**

McDougle CJ. Archives of General Psychiatry, 1998: 55(7): 633-641.

Risperidone and Aggression

- **Open-label, non-blinded trial of 11 males (4 week and 4 month assessments)**
- **Ages Ranged 6 to 34 years old**
- **10 / 11 met criteria for mental retardation**
- **Response noted: decreased aggression, self-injury, explosivity, overactivity, poor sleep hygiene**
- **Risperidone Dose Ranged 0.5 to 1.5 mg / day**
- **Weight Gain = 0.47 kg/week**

Horrigan JP. Journal of Autism and Developmental Disorders, 1997: 27(3): 313-324.

Olanzapine and Autism

- 3-month, open-label, open-dosage study
  - N = 25
  - Aged 6 to 16 years
  - Autistic or PDD NOS
- Responders (n = 23)
  - Irritability, hyperactivity, excessive speech
  - Communication skills improved
- Final Mean Dose = 10.7 mg/day
- Side Effects
  - Weight gain (5.8 kg), increased appetite, loss of strength, EPS

Kemner C. J Clin Psychopharmacology, 2002: 22(5): 455-460.

Quetiapine and Adolescent Autism

- 16-week, open label trial
- N = 6, Mean Age = 10.9 years
- Adolescents with mental retardation
- 2/6 completed 16 weeks
- Poorly tolerated at dose of 100-350 mg/day
  - Sedation, behavioral activation, weight gain, increased appetite

Martin A. J Child Adolescent Psychopharmacology, 1999: 9(2): 99-107.

Autism and Depressive Symptoms

Depression Expressed in Autism

- Irritability
- Sadness
- Aggression
- Suicidal

Ghaziuddin M. Journal of Autism and Developmental Disorders, 2002: 32(4): 299-306.

Fluvoxamine and Autism

- Reduced aggression, maladaptive behavior, and OCD symptoms (Adults)
  - Improved social relatedness (language)
- Discouraging Results in Childhood Study
  - Dosed 25 – 250 mg /day (106.9 mg/day)
  - 14/34 experience adverse effects
    - Insomnia, motor hyperactivity, agitation, aggression

McDougle CJ. Arch Gen Psychiatry 1996; 53: 1001-1008.

Antidepressant Data

- Clomipramine
  - Better efficacy vs. desipramine
    - Dose Range 50 – 200 mg / day
    - Stereotypy, anger, compulsions, SIB
- Fluvoxamine
- Fluoxetine
  - Case Reports of Doses 10 – 80 mg/day
  - Frequent hyperactivity, agitation, aggression
- Sertraline
- Paroxetine

Autism and Hyperactivity / Impulsivity

Pharmacotherapy of Hyperactivity in Autism

- Reviewed 41 Studies
  - Antipsychotics (n=13) [haloperidol and risperidone]
  - Antidepressants (n=3) [clomipramine, desipramine]
    - Fluoxetine improved lethargy / increased hyperactivity
  - Anxiolytics (n=4) [buspirone effective, diazepam not]
  - Stimulants (n=10) [MPH and d-amphetamine]
    - Attention, social responsiveness, decreased irritability, hyperactivity improved
    - Others report overactivity, anxiety, fear, agitation, tics worse
  - Alpha-2 Agonists (n=2) [clonidine]
  - Opiate Blockers (n=7) [naltrexone]
- Hyperactive symptoms reduced best with antipsychotics, stimulants, and naltrexone.

Aman MG. J Autism and Development Disoders, 2000: 30(5).

Autism and Self-Injury

Naltrexone and Autism

- **Autistic children, 8 males, mean age 4 yrs 4 months**
- **8 week cross-over study (Phase I and Phase II)**
  - **Attention difficulty, poor social relatedness, impaired communication skills**
- **Naltrexone dosed at 1.5 mg/kg every other day**
  - **2 patients dropped out due to administration problems**
  - **4/6 showed increased social initiations**
  - **5/6 showed reduced stereotypy**
  - **4/6 showed improved attention**
- **Well tolerated**

Williams PG, et al. Journal of Autism and Developmental Disorders, 2001: 31(1): 103-108.

Autism and Mood Stabilization

Mood Stabilizer Pharmacologic Management of Bipolar Disorder

- Lithium carbonate immediate release (Lithotab®)
- Lithium carbonate extended release (Lithobid®, Eskalith®)
- Lithium citrate
- Valproic acid (Depakote®, Depakene®)
- Carbamazepine (Tegretol®, Tegretol XR®)

American Psychiatric Association Practice Guidelines, 1994.
AACAP Practice Parameters. *J Am Acad Child Adolesc Psychiatry* 1997; 36(1).
Sachs GS. J Clin Psychopharmacol, 1996.
Kowatch RA. *J Am Acad Child Adolesc Psychiatry* 2000; 39(6).
Donovan SJ. *Am J Psychiatry* 2000; 157(5).

Additional Treatments for Bipolar Disorder

- Benzodiazepines
- Antidepressants
- Antipsychotics
- Propranolol
- Calcium channel blockers
- Adrenergic agonists
- Propranolol
- Electroconvulsive treatment (ECT)

Drug Interactions

Interactions Commonly Seen in Children

- Cigarette Smoking and Olanzapine/Antipsychotics
- Carbamazepine and Olanzapine
- Fluvoxamine / Ciprofloxacin and Clozapine
- Clozapine and Benzodiazepines
- Risperidone and CYP2D6 Inhibitors
- Olanzapine and Fluvoxamine
- Pimozide and Clarithromycin (1 sudden death report)
- Clonidine and Methylphenidate (4 sudden death reports)
- Imipramine and Methylphenidate
- MAOI / Decongestants and Methylphenidate (+ other stimulants)

"Red Flags" of Psychotropic Use in Children

Rapid Neuroleptization

- "More is Better" approach
- Giving elevated acute doses to produce rapid remission of psychotic symptoms.
- We now know: Antipsychotic relief is not sped up or supported by high initial doses.

Restraint and Seclusion

- Only to be used as safety measures.
- Need proper documentation of why a patient is receiving treatment without their permission.
- OBRA
  - Requires residents of long-term care facilities to be free from “unecessary physical or chemical restraints imposed for discipline or convenience.”
- HCFA
  - “A drug used as a restraint is a medication used to control behavior or to restrict the patient’s freedom of movement and is not a standard treatment for the patient’s medical or psychiatric condition.”

Unnecessary Drug

- Excessive Dose
- Excessive Duration
- Inadequate Monitoring
- Inadequate Indication
- Presence of Adverse Events
- Given in Duplication

QUESTIONS ??